SUPPORTING INFORMATION

The N-Acyloxyiminium Ion Aza-Prins Route to 1- Octahydroindoles: Total Synthesis and Structural Confirmation of the Antithrombotic Marine Natural Product Oscillarin

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Supplemental Information

1. Experimental procedures (32 pages)
2. ¹H and ¹³C spectra (37 pages)
3. X-ray crystal structure data (48 pages)

General information

Solvents were distilled under positive pressure of dry argon before use and dried by standard methods; THF and ether, from Na/benzophenone; and CH₂Cl₂, from CaCl₂. All commercially available reagents were used without further purification. All reactions were performed under nitrogen atmosphere. NMR (¹H, ¹³C) spectra were recorded on AMX-300, ARX-400, AV-400 and DMX-600 spectrometers. Low- and high-resolution mass spectra were recorded on VG Micromass, AEI-MS 902 or Kratos MS-50 spectrometers using fast atom bombardement (FAB) or electrospray techniques. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter in a 1 dm cell at ambient temperature. Analytical thin-layer chromatography was performed on Merck 60F₂₅₄ pre-coated silica gel plates. Visualization was performed by ultraviolet light and/or by staining with ceric ammonium molybdate, ninhydrine or potassium permanganate. Flash column chromatography was performed using (40-60 μm) silica gel at increased pressure.

Trifluoromethanesulfonic acid but-3-enyl ester. To a solution of pyridine (5.63 mL, 69.7 mmol) in CH₂Cl₂ (60 mL) at -78°C, was added Tf₂O (9.78 mL, 58.1 mmol), the mixture was stirred for 15 min. and 3-butenol (5.00 mL, 58.1 mmol) was added dropwise. After stirring for 20 min., the mixture was diluted with CH₂Cl₂, washed with ice cooled HCl 1N (40 mL), water and dried over Na₂SO₄. The solvent was removed under vacuum (without heating) and the resulting oil was purified on a small pad of silica gel (Hexanes/Et₂O 5:1) to give the corresponding triflate (8.18 g, 69%) as a light brown oil; ¹H RMN (400 MHz, CDCl₃) δ 5.82-5.65 (m, 1H), 5.25-5.20 (m, 2H), 4.57 (t, 2H, J=6.6 Hz), 2.62-2.57 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 131.4, 120.0, 76.5, 33.9.

(2S,4S)-2-But-3-enyl-4-*tert*-butoxycarbonylamino-pentanedioic acid dimethyl ester (4). To a solution of *N*-Boc-glutamic acid dimethylester **3** (4.72 g, 17.1 mmol) in THF (100 mL) at -78°C , was added LiHMDS (36.0 mL, 1.0 N in THF), stirred for 45 min. and a solution of 3-butenol-*O*-Tf prepared (7.0 g, 34 mmol) in THF (35 mL) at -78°C was added dropwise *via canula*. After stirring for 20 min., the solution was quenched with NH_4Cl (2N), warmed up to RT, concentrated under vacuum. The resulting aqueous solution was extracted with CH_2Cl_2 , the combined organic extracts were washed with brine and dried over Na_2SO_4 . The solvent was removed under vacuum and the resulting oil was purified by flash chromatography (EtOAc/Hexanes 1:9 to 15:85) to give **4** (4.80 g, 85%) as a colourless oil; ^1H RMN (400 MHz, CDCl_3) δ 5.80-5.65 (m, 1H), 5.00-5.92 (m, 2H), 4.20-4.15 (m, 1H), 3.71 (s, 3H), 3.66 (s, 3H), 2.55-2.45 (m, 1H), 2.10-1.95 (m, 4H), 1.78-1.70 (m, 1H), 1.65-1.58 (m, 1H), 1.43 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 176.5, 173.4, 155.7, 137.7, 115.9, 80.4, 52.9, 52.8, 52.2, 41.9, 34.8, 31.9, 31.5, 28.7; $[\alpha]_D^{25}$: $+12.9^{\circ}$ (c 1.18, CHCl_3); HRMS for $\text{C}_{16}\text{H}_{28}\text{NO}_6$ calculated ($\text{M} + \text{H}^+$) 330.19165 found 330.19050.

(2S,4S)-4-But-3-enyl-5-oxo-pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-methyl ester (5). Compound **4** (4.80 g, 14.6 mmol) was dissolved in HCO_2H (37 mL) and stirred at RT until no trace of starting material (approximately 5h), concentrated under vacuum, the resulting oil was dissolved in toluene (180 mL) and heated at reflux for 1.5h. The solution was concentrated under vacuum to give the corresponding lactam as a colourless oil; ^1H RMN (400 MHz, CDCl_3) δ 6.65-6.60

(broad s, 1H), 5.80-5.70 (m, 1H), 5.00-4.90 (m, 2H), 4.08 (t, 1H, $J=9.2$ Hz), 3.78 (s, 3H), 2.70-2.58 (m, 1H), 2.45-2.38 (m, 1H), 2.20-1.82 (m, 3H), 1.82-1.75 (m, 1H), 1.42-1.35 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 179.5, 172.7, 138.0, 115.8, 54.1, 53.0, 40.8, 31.8, 31.7, 30.4; $[\alpha]_D$: $+16.1^\circ$ (c 1.5, CHCl_3); HRMS for $\text{C}_{10}\text{H}_{15}\text{NO}_3$ calculated 197.105194 found 197.104977. To a solution of the lactam obtained in CH_2Cl_2 (40 mL), was added successively Et_3N (6.09 mL, 43.7 mmol), Boc_2O (4.77 g, 21.9 mmol) followed by DMAP (cat.). After stirring overnight, the solution was quenched with NH_4Cl (2N), the aqueous layer was extracted with CH_2Cl_2 , the combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The crude oil obtained was purified by flash chromatography (EtOAc/Hexanes 10:90 to 15:85) to give **5** (3.55 g, 82%) as a colourless oil; ^1H RMN (400 MHz, CDCl_3) δ 5.80-5.70 (m, 1H), 5.10-4.95 (m, 2H), 4.55-4.45 (m, 1H), 3.76 (s, 3H), 2.60-2.42 (m, 2H), 2.21-1.95 (m, 3H), 1.63-1.58 (m, 1H), 1.45-1.40 (m, 10H); ^{13}C NMR (100 MHz, CDCl_3) δ 175.4, 172.4, 149.0, 137.6, 116.1, 84.0, 57.8, 52.9, 42.2, 31.5, 30.5, 28.3, 28.2; $[\alpha]_D$: $+12.9^\circ$ (c 1.18, CHCl_3); HRMS for $\text{C}_{15}\text{H}_{24}\text{NO}_5$ calculated ($\text{M} + \text{H}^+$) 298.16544 found 298.16450.

(2S,4S)-5-Acetoxy-4-but-3-enyl-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester (6). To a solution of **5** (3.00 g, 10.0 mmol) in THF (70 mL) at -78°C , was added a solution of LiHBEt_3 (11.1 mL, 1.0 N in THF), stirred for 1h, quenched with NaHCO_3 (sat.), 2 drops of H_2O_2 (30% in H_2O) were added and the solution was concentrated under vacuum. The resulting oil was dissolved in CH_2Cl_2 (25 mL) and Et_3N (2.81 mL, 20.2 mmol), Ac_2O (2.86 mL, 30.3 mmol) and DMAP (cat.) were added successively. After stirring overnight, the solution was quenched with NaHCO_3 (sat.), the aqueous layer was extracted with CH_2Cl_2 , the combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The crude oil obtained was purified by flash chromatography

(EtOAc/Hexanes 15:85) to give the corresponding hemiaminal derivative **6** (3.13 g, 91%) as a mixture of diastereoisomers.

(2S,3aS,6S,7aS)-6-Bromo-2,3,3a,4,5,6,7,7a-octahydroindole-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester (7). To a solution of the hemiaminal derivative (0.800 g, 2.34 mmol) in CH₂Cl₂ (15 mL) at -78°C, was added a solution of SnBr₄ (3.04 mL, 1.0 M in CH₂Cl₂) dropwise. After stirring for 10 min., the solution was quenched with NaHCO₃ (sat.), warmed up to RT, filtered on a small celite pad, the filtrate was washed with brine, dried over Na₂SO₄ and concentrated under vacuum. The crude oil obtained was purified by flash chromatography (EtOAc/Hexanes 10:90 to 15:85) to give **7** (0.660 g, 78%) as a colourless oil; ¹H RMN (400 MHz, DMSO-d₆) δ (mixture of rotamers) 4.21-4.08 (m, 2H), 3.85-3.79 (m, 1H), 3.67 (s, 1.5H), 3.64 (s, 1.5H), 2.62-2.41 (m, 1H), 2.39-2.21 (m, 1H), 2.17-1.60 (m, 7H), 1.37 (s, 4.5H), 1.30 (s, 4.5H); ¹³C NMR (100 MHz, DMSO-d₆) δ (mixture of rotamers) 174.3, 173.8, 153.6, 152.9, 80.0, 79.9, 59.7, 59.3, 58.0, 57.6, 52.8, 52.7, 50.1, 50.0, 39.6, 35.6, 35.0, 32.7, 32.6, 32.3, 31.5, 29.0, 28.7, 25.6; [α]_D: +5.9° (c 1.5, CHCl₃); HRMS for C₁₅H₂₄NO₄Br calculated 361.088870 found 361.088652.

(2S,3aS,6S,7aS)-6-Chloro-2,3,3a,4,5,6,7,7a-octahydroindole-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester (7a). Same procedure than **7**. (66%); ¹H RMN (400 MHz, DMSO-d₆) δ (mixture of rotamers) 4.20-4.15 (m, 1H), 4.05-3.92 (m, 1H), 3.85-3.75 (m, 1H), 3.64 (s, 1.5H), 3.61 (s, 1.5H), 2.42-2.20 (m, 2H), 2.16-2.05 (m, 1H), 1.95-1.80 (m, 2H), 1.75-1.60 (m, 4H), 1.17 (s, 4.5H), 1.13 (s, 4.5H); ¹³C NMR (100 MHz, DMSO-d₆) δ (mixture of rotamers) 174.4, 173.9, 153.8, 153.1, 80.1, 59.9,

58.0, 57.9, 57.8, 57.4, 52.9, 52.8, 39.3, 39.2, 38.9, 35.9, 35.2, 32.5, 32.0, 31.7, 29.1, 28.9, 24.8; $[\alpha]_D$: +2.0° (c 0.98, CHCl₃); HRMS for C₁₅H₂₅NO₄Cl calculated (M + H⁺) 318.14860 found 318.14722.

7a-epi

(2S,3aS,6R,7aS)-6-Chloro-2,3,3a,4,5,6,7,7a-octahydroindole-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester (7a-epi). (5%); ¹H RMN (400 MHz, DMSO-d₆) δ (mixture of rotamers) 4.55-4.48 (m, 1H), 4.21-4.12 (m, 1H), 3.90-3.80 (m, 1H), 3.65 (s, 1.5 H), 3.61 (s, 1.5 H), 2.33-1.80 (m, 4H), 1.75-1.60 (m, 3H), 1.50-1.22 (m, 11H); ¹³C NMR (100 MHz, DMSO-d₆) δ (mixture of rotamers) 174.3, 173.8, 170.5, 153.6, 152.9, 79.8, 79.7, 71.4, 71.3, 59.8, 59.3, 57.0, 56.6, 55.7, 52.8, 52.7, 36.2, 35.6, 33.9, 33.6, 32.4, 31.7, 31.6, 28.9, 28.7, 26.5, 22.9, 21.8; $[\alpha]_D$: -42.7° (c 1.09, CHCl₃); HRMS for C₁₅H₂₄NO₄Cl calculated 317.139386 found 317.140307.

(2S,4S)-4-But-3-enyl-5-oxo-pyrrolidine-1,2-dicarboxylic acid 1-benzyl ester 2-methyl ester. To a solution of the lactam (0.567 g, 2.87 mmol) in THF (7 mL) at -78°C, was added dropwise a solution of LiHMDS (3.2 mL, 1.0 M in THF). After stirring for 30 min., Cbz-Cl (0.45 mL, 3.16 mmol) was added and the resulting mixture was stirred for 1h. The solution was quenched with NH₄Cl (2N), warmed up to RT, concentrated under vacuum, the residue was dissolved in H₂O/CH₂Cl₂, the aqueous phase was extracted with CH₂Cl₂, the combined organic extracts were washed with brine, dried over Na₂SO₄ and concentrated under vacuum. The crude oil obtained was purified by flash chromatography (EtOAc/Hexanes 25:75) to give *N*-protected lactam (0.783 g, 82%) as a colourless oil; ¹H RMN (400 MHz, CDCl₃) δ 7.41-7.25 (m, 5H), 5.82-5.68 (m, 1H), 5.33 (d, 1H, J=12.3 Hz), 5.20 (d, 1H, J=12.3 Hz), 5.08-4.96

(m, 2H), 4.58-4.48 (m, 1H), 3.65 (s, 3H), 2.61-2.47 (m, 2H), 2.22-1.95 (m, 3H), 1.78-1.62 (m, 1H), 1.58-1.42 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 175.1, 172.1, 151.5, 137.5, 135.3, 129.0, 128.9, 128.6, 116.3, 68.8, 57.6, 53.0, 42.1, 31.5, 30.5, 28.3; $[\alpha]_D$: -19.5° (c 1.25, CHCl_3); HRMS for $\text{C}_{18}\text{H}_{22}\text{NO}_5$ ($\text{M}+\text{H}^+$) calculated 332.149798 found 332.148500.

(2S,3aS,6S,7aS)-6-Chloro-2,3,3a,4,5,6,7,7a-octahydroindole-1,2-dicarboxylic acid 1-benzyl ester 2-methyl ester (7b). Same procedure than compound **6** for reduction/acetylation (80%) and than compound **7** for cyclization (60%); ^1H RMN (400 MHz, CDCl_3) δ (mixture of rotamers) 7.40-7.22 (m, 5H), 5.20-4.95 (m, 2H), 4.38-4.23 (m, 1H), 4.10-4.00 (m, 0.5H), 3.99-3.90 (m, 0.5H), 3.80-3.62 (m, 2.5H), 3.57 (s, 1.5H), 2.77-2.62 (m, 0.5H), 2.60-2.50 (m, 0.5H), 2.40-2.28 (m, 1H), 2.23-2.17 (m, 1H), 2.10-1.60 (m, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ (mixture of rotamers) 173.6, 173.4, 154.6, 154.0, 136.8, 136.7, 129.0, 128.8, 128.6, 128.5, 128.4, 128.3, 67.7, 67.5, 59.7, 59.5, 58.0, 57.6, 56.4, 52.8, 52.6, 38.6, 38.1, 36.0, 35.4, 32.7, 31.7, 31.6, 31.5, 24.9, 24.8; $[\alpha]_D$: -7.3° (c 1.2, CHCl_3); HRMS for $\text{C}_{18}\text{H}_{23}\text{ClNO}_4$ ($\text{M}+\text{H}^+$) calculated 352.131561 found 352.132100.

(2S,3aS,6S,7aS)-6-Bromo-2,3,3a,4,5,6,7,7a-octahydroindole-1,2-dicarboxylic acid 1-benzyl ester 2-methyl ester (7c). Same procedure than compound **6** for reduction/acetylation (80%) and than compound **7** for cyclization (61%); ^1H RMN (400 MHz, CDCl_3) δ (mixture of rotamers) 7.42-7.24 (m, 5H), 5.21-4.97 (m, 2H), 4.38-

4.23 (m, 1H), 4.07-4.00 (m, 0.5H), 3.98-3.70 (m, 3H), 3.56 (s, 1.5H), 2.85-2.75 (m, 0.5H), 2.70-2.60 (m, 0.5H), 2.40-2.30 (m, 1H), 2.28-1.92 (m, 4H), 1.90-1.65 (m, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ (mixture of rotamers) 173.0, 172.8, 154.0, 153.4, 136.3, 136.1, 128.4, 128.3, 128.0, 127.9, 127.7, 67.1, 67.0, 59.1, 59.0, 57.8, 57.4, 52.3, 52.0, 46.8, 38.9, 38.3, 35.4, 34.7, 32.2, 31.9, 31.7, 31.1, 25.4, 25.3; $[\alpha]_D$: +5.2° (c 1.0, CHCl_3); HRMS for $\text{C}_{16}\text{H}_{23}\text{BrNO}_4$ ($\text{M}+\text{H}^+$) calculated 396.081045 found 396.079720.

(2S,4S)-4-But-3-enyl-5-oxo-pyrrolidine-1,2-dicarboxylic acid dimethyl ester. To a solution of the lactam (0.503 g, 2.55 mmol) in THF (7 mL) at -78°C , was added dropwise a solution of LiHMDS (2.8 mL, 1.0 M in THF). After stirring for 30 min., methylchloroformate (0.22 mL, 2.81 mmol) was added and the resulting mixture was stirred for 1h. The solution was quenched with NH_4Cl (2N), warmed up to RT, concentrated under vacuum, the residue was dissolved in $\text{H}_2\text{O}/\text{CH}_2\text{Cl}_2$, the aqueous phase was extracted with CH_2Cl_2 , the combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The crude oil obtained was purified by flash chromatography (EtOAc/Hexanes 25:75) to give *N*-protected lactam (0.570 g, 86%) as a colourless oil; ^1H RMN (300 MHz, CDCl_3) δ 5.80-5.60 (m, 1H), 5.05-4.90 (m, 2H), 4.60-4.50 (m, 1H), 3.80 (s, 3H), 3.73 (s, 3H), 2.60-2.45 (m, 2H), 2.20-1.90 (m, 3H), 1.70-1.60 (m, 1H), 1.50-1.40 (m, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 175.0, 172.1, 152.4, 137.5, 116.2, 57.6, 54.3, 53.1, 42.2, 31.4, 30.5, 28.2; $[\alpha]_D$: -2.4° (c 0.83, CHCl_3); HRMS for $\text{C}_{12}\text{H}_{17}\text{NO}_5$ calculated 255.110673 found 255.111221.

(2S,3aS,6S,7aS)-6-Chloro-2,3,3a,4,5,6,7,7a-octahydroindole-1,2-dicarboxylic acid dimethyl ester (7d). Same procedure than compound 6 for reduction/acetylation (75%) and than compound 7 for cyclization (66%); ^1H RMN (400 MHz, CDCl_3) δ (mixture of rotamers) 4.38-4.22 (m, 1H), 4.05-3.98 (m, 0.4H), 3.95-3.82 (m, 0.6H), 3.80-3.60 (m, 7H), 2.70-2.61 (m, 0.4H), 2.58-2.50 (m, 0.6H), 2.38-2.25 (m, 1H), 2.23-2.15 (m, 1H), 2.10-1.93 (m, 2H), 1.90-1.60 (m, 4H); ^{13}C NMR (100 MHz, CDCl_3) δ (mixture of rotamers) 173.5, 173.4, 155.2, 154.7, 59.7, 59.4, 58.1, 57.7, 56.4, 53.0, 52.7, 38.6, 38.1, 36.0, 35.3, 32.8, 31.8, 31.7, 31.6, 24.9, 24.9; $[\alpha]_D$: -7.6° (c 0.83, CHCl_3); HRMS for $\text{C}_{12}\text{H}_{18}\text{ClNO}_4$ calculated 275.092436 found 275.093231.

(2S,3aS,6S,7aS)-6-Bromo-2,3,3a,4,5,6,7,7a-octahydroindole-1,2-dicarboxylic acid dimethyl ester (7e). Same procedure than compound 6 for reduction/acetylation (75%) and than compound 7 for cyclization (72%); ^1H RMN (400 MHz, CDCl_3) δ (mixture of rotamers) 4.35-4.20 (m, 1H), 4.05-3.97 (m, 0.4H), 3.90-3.60 (m, 7.6H), 2.80-2.72 (m, 0.4H), 2.70-2.61 (m, 0.6H), 2.40-2.28 (m, 1H), 2.22-1.90 (m, 4H), 1.87-1.67 (m, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ (mixture of rotamers) 173.5, 173.4, 155.1, 154.7, 59.6, 59.4, 58.4, 58.0, 53.0, 52.7, 47.3, 39.5, 38.9, 35.9, 35.2, 32.8, 32.4, 32.3, 31.8, 26.0, 25.8; $[\alpha]_D$: $+7.4^\circ$ (c 1.15, CHCl_3); HRMS for $\text{C}_{12}\text{H}_{18}\text{BrNO}_4$ calculated 319.041919 found 319.042297.

(2S,3aS,6R,7aS)-6-Acetoxy-2,3,3a,4,5,6,7,7a-octahydroindole-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester (8). To a solution of 7 (0.500 g, 1.38 mmol) in toluene (12 mL), was added Bu_4NOAc (6.20 g, 20.7 mmol) and the mixture was

heated at 40-50°C for 2h. After cooled down at RT, the solution was diluted with Hexanes, the organic solution was washed with H₂O, brine and dried over Na₂SO₄. The solvent was removed under vacuum and the resulting oil was purified by flash chromatography (EtOAc/Hexanes 15:85) to give **8** (0.368 g, 78%) as a colourless oil; ¹H RMN (400 MHz, DMSO-d₆) δ 4.97-4.90 (m, 1H), 4.22-4.12 (m, 1H), 3.95-3.82 (m, 1H), 3.67 (s, 3H), 2.40-2.28 (m, 1H), 2.20-2.10 (m, 2H), 2.05 (s, 3H), 1.96-1.80 (m, 2H), 1.66-1.47 (m, 4H), 1.30 (s, 9H); ¹³C NMR (100 MHz, DMSO-d₆) δ 174.3, 170.6, 79.7, 69.8, 59.7, 59.2, 53.9, 52.7, 36.3, 35.8, 32.5, 31.9, 30.9, 28.7, 24.0, 21.8, 20.4; [α]_D: -47.5° (c 1.55, CHCl₃); HRMS for C₁₇H₂₈NO₆ calculated (M + H⁺) 342.191663 found 342.193100.

O-MOM-D-Pla-OMe. To a suspension of D-Phenyllactic acid (0.460 g, 2.78 mmol) in Et₂O (15 mL), was added CH₂N₂ until a yellow colour and the solution was concentrated under vacuum. The resulting residue was dissolved in CH₂Cl₂ (8 mL) and ⁱPr₂NEt (1.46 mL, 8.32 mmol) followed by MOMCl (0.64 mL, 8.32 mmol) were added. After stirring overnight, N₂ was bubbled into the solution for 15 min., quenched with NH₄Cl (sat.), the aqueous phase was extracted with CH₂Cl₂, the combined organic phases were washed with brine and dried over Na₂SO₄. The solvent was removed under vacuum and the resulting oil was purified by flash chromatography (EtOAc/Hexanes 25:75) to give the corresponding O-protected methyl ester (0.460 g, 90%) as white solid; ¹H RMN (400 MHz, CDCl₃) δ 7.32-7.20 (m, 5H), 4.57 (dd, 2H, J=7.0 Hz, J=48.8 Hz), 4.34 (dd, 1H, J=4.4 Hz, J=9.0 Hz), 3.72 (s, 3H), 3.18-3.05 (m, 4H), 3.00-2.94 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 172.9, 137.4, 129.9, 128.8, 127.1, 96.4, 76.7, 56.1, 52.4, 39.6; [α]_D: +57.7° (c 0.77, CHCl₃); HRMS for C₁₂H₁₇NO₄ (M + H⁺) calculated 225.112684 found 225.112327.

O-MOM-D-Ple-D-Phe-OBn. To a solution of the methyl ester (0.442 g, 1.97 mmol) in THF/H₂O (8 mL, 5:3), was added LiOH (0.142 g, 5.91 mmol) and the solution was stirred for 1h. The mixture was cooled down at 0°C, neutralized to pH=5 with HCl (2N), the aqueous phase was extracted with EtOAc, the combine organic extracts were washed with brine and dried over Na₂SO₄ to give the corresponding carboxylic acid as a white solid (0.410 g, quant.); ¹H RMN (400 MHz, CDCl₃) δ 10.35-10.10 (broad s, 1H), 7.35-7.20 (m, 5H), 4.60 (dd, 2H, J=6.9 Hz, J=64.0 Hz), 4.40 (dd, 1H, J=3.6 Hz, J=9.1 Hz), 3.20 (dd, 1H, J=10.3 Hz, J=14.0 Hz), 3.10-2.98 (m, 4H); ¹³C NMR (100 MHz, CDCl₃) δ 177.8, 137.3, 129.9, 128.8, 127.2, 96.5, 76.6, 56.2, 39.4; [α]_D: +47.8° (c 0.80, CHCl₃). To a solution of the acid obtained (0.410 g, 1.97 mmol) in CH₂Cl₂ (5 mL) at 0°C, was added successively EDC (0.486 g, 2.56 mmol), HOBT (0.343 g, 2.56 mmol), stirred for 10 min., a solution of D-Phe-OBn (0.834 g, 1.97 mmol) and Et₃N (0.54 mL, 3.94 mmol) in CH₂Cl₂ (2 mL) was added and the resulting mixture was stirred overnight at RT. The solution was diluted with CH₂Cl₂, washed with NaHCO₃ (sat.), brine and dried over Na₂SO₄. The solvent was removed under vacuum and the resulting oil was purified by flash chromatography (CH₂Cl₂/MeOH 100:0 to 95:5) to give the corresponding pseudo-dipeptide (0.770 g, 89%) as a white solid; ¹H RMN (400 MHz, CDCl₃) δ 7.42-7.18 (m, 12H), 6.97 (d, 1H, J=8.6 Hz), 6.82 (dd, 2H, J=1.3 Hz, J=6.8 Hz), 5.12 (dd, 2H, J=12.1 Hz, J=21.1 Hz), 5.00-4.95 (m, 1H), 4.45 (dd, 2H, J=6.8 Hz, J=34.1 Hz), 4.32 (dd, 1H, J=3.6 Hz, J=7.7 Hz), 3.10-3.02 (m, 5H), 3.00-2.85 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 171.5, 171.4, 137.5, 135.9, 135.4, 130.3, 129.8, 129.1, 129.0, 128.9, 128.7, 127.5, 127.2, 96.2, 78.0, 67.7, 56.3, 52.7, 39.3, 38.5; [α]_D: +33.7° (c 1.0, CHCl₃); HRMS for C₂₇H₃₀NO₅ (M + H⁺) calculated 448.212398 found 448.212031.

O-MOM-D-Ple-D-Phe-OH (9). To a solution of the pseudo-dipeptide (0.533 g, 1.19 mmol) in MeOH/EtOAc (10 mL, 1:1), was added Pd/C 10% (cat.) and stirred under 1 atm. of H₂ overnight. The catalyst was filtered through a celite pad, the filtrate was concentrated to give the corresponding acid **9** (0.420 g, quant.) as a white solid; ¹H

RMN (400 MHz, CDCl_3) δ 9.30-8.80 (broad s, 1H), 7.45-7.08 (m, 8H), 7.07 (d, 1H, $J=8.5$ Hz), 7.00-6.92 (m, 2H), 4.95 (dd, 1H, $J=2.8$ Hz, $J=5.8$ Hz), 4.47 (dd, 2H, $J=6.7$ Hz, $J=35.8$ Hz), 4.35 (dd, 1H, $J=3.4$ Hz, $J=7.8$ Hz), 3.18-3.00 (m, 6H), 2.95-2.78 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 174.7, 172.5, 137.3, 135.8, 130.3, 129.8, 129.0, 128.7, 127.6, 127.2, 96.3, 78.0, 56.4, 52.7, 39.4, 38.0; $[\alpha]_D$: +4.6° (c 0.89, CHCl_3); HRMS for $\text{C}_{20}\text{H}_{24}\text{NO}_5$ calculated 358.165448 found 358.164294.

(2S,3aS,6R,7aS)-6-Acetoxy-2,3,3a,4,5,6,7,7a-octahydroindole-1-(D-Phe-D-Pla-OMOM)-2-carboxylic acid methyl ester. To a solution of **8** (0.130 g, 0.285 mmol) in CH_2Cl_2 (2 mL), was added TFA (0.55 mL, 7.10 mmol) and stirred at RT for 30 min. The solution was concentrated under vacuum, the resulting residue was dissolved in CH_2Cl_2 (2 mL), cooled down at 0°C and EDC (0.060 g, 0.37 mmol) followed by HOBt (0.042 g, 0.37 mmol) were added successively. After stirring for 10 min., a solution of **9** (0.102 g, 0.285 mmol) and Et_3N (0.20 mL, 1.40 mmol) in CH_2Cl_2 (2 mL) was added and the resulting mixture was stirred overnight at RT. The solution was diluted with CH_2Cl_2 , washed with NaHCO_3 (sat.), brine and dried over Na_2SO_4 . The solvent was removed under vacuum and the resulting oil was purified by flash chromatography (EtOAc/Hexanes 1:1) to give the corresponding pseudo-tripeptide (0.150 g, 91%) as colourless oil; ^1H RMN (400 MHz, CDCl_3) δ 7.32-7.15 (m, 10H), 5.00-4.95 (m, 1H), 4.90-4.82 (m, 1H), 4.52 (d, 1H, $J=6.8$ Hz), 4.45 (d, 1H, $J=6.8$ Hz), 4.29 (dd, 1H, $J=3.5$ Hz, $J=7.9$ Hz), 4.19 (dd, 1H, $J=8.1$ Hz, $J=10.1$ Hz), 3.66 (s, 3H), 3.32-3.22 (m, 1H), 3.20-3.11 (m, 4H), 2.95-2.84 (m, 2H), 2.78-2.70 (m, 1H), 2.18-2.05 (m, 4H), 2.02-1.93 (m, 2H), 1.81-1.50 (m, 5H), 1.41-1.25 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 172.8, 171.3, 170.4, 169.5, 137.6, 136.9, 130.2, 129.8, 128.9, 128.6, 127.4, 127.0, 96.6, 78.3, 69.3, 59.2, 56.5, 54.6, 52.6, 51.9, 40.6, 39.6, 36.8, 31.2, 30.5, 23.3, 21.7, 19.8;

$[\alpha]_D$: +9.3° (c 1.2, CHCl₃); HRMS for C₃₂H₄₁N₂O₈ (M + H⁺) calculated 581.286292 found 581.285916.

(2S,3aS,6R,7aS)-6-(2-Methoxymethoxy)-2,3,3a,4,5,6,7,7a-octahydroindole-1-(D-Phe-D-Pla-OMOM)-2-carboxylic acid methyl ester (10). To a solution of the O-acetyl-L-Choi derivative (0.150 g, 0.258 mmol) in MeOH (3 mL), was added a freshly prepared solution of NaOMe (3 mL, 0.6 N in MeOH). After stirring for 4h, the solution was neutralized by addition of acidic resin Amberlite IR-120(plus), filtered and concentrated under vacuum to give the corresponding alcohol (0.139 g, quant.) as a colourless oil; ¹H RMN (400 MHz, CDCl₃) δ 7.32-7.15 (m, 10H), 5.00-4.85 (m, 1H), 4.52 (d, 1H, J=6.9 Hz), 4.45 (d, 1H, J=6.9 Hz), 4.29 (dd, 1H, J=3.4 Hz, J=7.9 Hz), 4.18-4.05 (m, 2H), 3.66 (s, 3H), 3.63-3.56 (m, 1H), 3.18-3.05 (m, 4H), 2.95-2.70 (m, 4H), 2.18-2.05 (m, 1H), 2.01-1.75 (m, 3H), 1.63-1.50 (m, 3H), 1.44-1.35 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 172.9, 171.4, 169.2, 137.5, 136.5, 130.2, 129.9, 128.9, 128.6, 127.4, 127.1, 96.5, 78.2, 65.8, 59.1, 56.6, 54.7, 52.5, 51.4, 40.5, 39.6, 37.0, 34.2, 30.6, 26.0, 19.3; $[\alpha]_D$: +23.2° (c 1.0, CHCl₃); FAB for C₃₀H₃₉N₂O₇ (M + H⁺) calculated 539.3 found 539.0. To a solution of the alcohol obtained (0.139 g, 0.258 mmol) in CH₂Cl₂ (5 mL), was added successively ⁱPr₂NEt (0.13 mL, 0.77 mmol) and MOMCl (58 μL, 0.77 mmol). After stirring overnight, N₂ was bubbled into the solution for 15 min., quenched with NH₄Cl (sat.), the aqueous phase was extracted with CH₂Cl₂, the combined organic phases were washed with brine and dried over Na₂SO₄. The solvent was removed under vacuum and the resulting oil was purified by flash chromatography (EtOAc/Hexanes 1:1) to give **10** (0.120 g, 80%) as a white solid which crystallise from Hexanes/EtOAc; ¹H RMN (400 MHz, CDCl₃) δ 7.35-7.18 (m, 10H), 5.00-4.95 (m, 1H), 4.70 (d, 1H, J=6.7 Hz), 4.66 (d, 1H, J=6.7 Hz), 4.51 (d,

1H, $J=6.9$ Hz), 4.43 (d, 1H, $J=6.9$ Hz), 4.28 (dd, 1H, $J=3.4$ Hz, $J=8.0$ Hz), 4.14 (dd, 1H, $J=8.1$ Hz, $J=10.0$ Hz), 3.83 (broad s, 1H), 3.65 (s, 3H), 3.50-3.40 (m, 4H), 3.20-3.05 (m, 4H), 2.95-2.82 (m, 2H), 2.75 (dd, 1H, $J=9.8$ Hz, $J=12.8$ Hz), 2.22-2.17 (m, 1H), 2.06-1.92 (m, 1H), 1.82-1.73 (m, 2H), 1.62-1.43 (m, 3H), 1.41-1.22 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 172.9, 171.2, 169.4, 137.6, 136.6, 130.2, 129.8, 128.9, 128.6, 127.4, 127.0, 96.5, 95.4, 78.3, 71.3, 59.1, 56.5, 55.9, 54.9, 52.5, 51.5, 40.6, 39.6, 36.8, 31.8, 30.6, 24.3, 19.8; $[\alpha]_D^{25}$: +18.3° (c 0.5, CHCl_3); mp: 120-122°C; HRMS for $\text{C}_{32}\text{H}_{43}\text{N}_2\text{O}_8$ ($M + \text{H}^+$) calculated 583.301942 found 583.302082.

D-Pla(OMOM)-D-Phe-L-CHOI(OMOM)-Adc(Boc₂) (12). To a solution of the methyl ester **10** (0.054 g, 0.093 mmol) in THF/ H_2O (5 mL/ 3 mL), was added LiOH (0.010 g, 0.41 mmol) and the solution was stirred for 7h. The mixture was cooled down at 0°C, neutralized to pH=5 with HCl (2N), the aqueous phase was extracted with CH_2Cl_2 , the combine organic extracts were washed with brine and dried over Na_2SO_4 to give the corresponding carboxylic acid as a white solid (0.050 g, quant.); ^1H RMN (400 MHz, CDCl_3) δ 7.40-7.05 (m, 10H), 5.05-4.95 (m, 1H), 4.68 (dd, 2H, $J=6.6$ Hz, $J=14.3$ Hz), 4.50 (d, 1H, $J=6.8$ Hz), 4.43 (d, 1H, $J=6.8$ Hz), 4.35-4.20 (m, 2H), 3.82 (s, 1H), 3.60-3.50 (m, 1H), 3.45 (s, 3H), 3.21-3.05 (m, 4H), 3.00-2.70 (m, 3H), 2.20-2.01 (m, 2H), 2.00 (m, 1H), 1.80-1.74 (m, 1H), 1.72-1.60 (m, 1H), 1.50-1.22 (m, 5H); ^{13}C NMR (100 MHz, CDCl_3) δ 174.0, 171.4, 171.3, 137.4, 136.2, 130.2, 129.8, 129.0, 128.6, 127.6, 127.1, 96.6, 95.4, 78.3, 71.2, 59.4, 56.5, 56.0, 51.6, 40.3, 39.6, 35.9, 31.6, 29.4, 24.1, 19.7; $[\alpha]_D^{25}$: -3.4° (c 1.25, CHCl_3); HRMS for $\text{C}_{31}\text{H}_{41}\text{N}_2\text{O}_8$ ($M + \text{H}^+$) calculated 569.286292 found 569.284400. To a solution of the acid obtained (0.043 g, 0.076 mmol), the amine **11** (0.045 g, 0.11 mmol) and $^i\text{Pr}_2\text{NEt}$ (42 μL , 0.30 mmol) in CH_2Cl_2 (3 mL) at 0°C, was added successively EDC (0.022 g, 0.11 mmol) and HOBT

(0.016 g, 0.11 mmol), stirred at 0°C for 1h and overnight at RT. The solution was quenched with NaHCO₃ (sat.), the aqueous layer was extracted with CH₂Cl₂, the combined organic extracts were washed with brine and dried over Na₂SO₄. The solvent was removed under vacuum and the resulting oil was purified by flash chromatography (EtOAc/Hexanes 85:15 to 100:0) to give **12** (0.060 g, 86 %) as a white solid; ¹H RMN (400 MHz, CD₃OD) δ 7.40-7.18 (m, 10H), 5.58 (s, 1H), 4.78-4.63 (m, 3H), 4.58 (d, 1H, *J*=6.8 Hz), 4.51 (d, 1H, *J*=6.8 Hz), 4.40-4.10 (m, 6H), 3.85 (s, 1H), 3.55-3.37 (m, 5H), 3.30-3.20 (m, 1H), 3.10 (s, 3H), 3.00-2.82 (m, 3H), 2.40-2.22 (m, 3H), 2.02-1.95 (m, 1H), 1.83-1.64 (m, 2H), 1.62-1.52 (m, 1H), 1.51-1.23 (m, 23H); ¹³C NMR (100 MHz, CD₃OD) δ 173.2, 173.1, 170.7, 152.0, 137.6, 136.7, 136.4, 129.9, 129.6, 128.8, 128.3, 127.3, 126.7, 96.0, 95.1, 77.8, 71.6, 60.6, 55.6, 55.3, 54.8, 53.1, 39.3, 38.4, 37.4, 36.5, 30.9, 28.2, 27.6, 26.8, 23.9, 19.4; [α]_D: -5.65° (c 1.45, CHCl₃); HRMS for C₄₈H₆₉N₆O₁₁ (M + H⁺) calculated 905.502433 found 905.504500.

Oscillarlin (2). To a solution of **12** (0.020 g, 0.022 mmol) in THF (1 mL), was added HCl (1 mL, 12 N) and the solution was stirred at RT for 4h. The mixture was concentrated under vacuum and the residue was lyophilized to give **2** (0.013 g, 90%) as a fluffy white solid, which is essentially pure by LC/MS analysis (R_T =17 min., MeCN/H₂O: 30% to 60% over 30 min. with 0.01% TFA, electrospray ionisation) on an analytical reverse phase column (C₁₈ Prevail Alltech, 4.6 X 250 mm). It can be further purified by preparative LC/MS using the same conditions (0.010 g, 70%); ¹H RMN (600 MHz, CD₃OD) δ 7.40-7.20 (m, 10H), 5.66 (d, 1H, J =1.4 Hz), 4.82–4.78 (m, 1H), 4.27 (dd, 1H, J =3.7 Hz, J =7.7 Hz), 4.24–4.18 (m, 4H), 4.15 (dd, 1H, J =8.5 Hz, J =16.9 Hz), 4.01 (s, 1H), 3.68-3.63 (m, 1H), 3.47-3.42 (m, 1H), 3.31-3.25 (m, 1H), 3.08 (dd,

1H, J=3.7 Hz, J=13.9 Hz), 2.95-2.80 (m, 3H), 2.50-2.38 (m, 2H), 2.20-2.12 (m, 1H), 2.02-1.97 (m, 1H), 1.90-1.75 (m, 2H), 1.65-1.58 (m, 1H), 1.55-1.49 (m, 1H), 1.48-1.40 (m, 2H), 1.39-1.33 (m, 1H); ¹³C NMR (150 MHz, CD₃OD) δ 174.7, 173.2, 170.6, 155.0, 137.9, 136.8, 136.1, 129.8, 129.6, 128.7, 128.2, 127.3, 126.6, 119.7, 72.8, 65.4, 60.6, 55.5, 55.3, 54.2, 52.5, 48.8, 40.7, 38.9, 37.4, 36.5, 33.0, 30.8, 28.4, 25.7, 18.8; [α]_D: +6.2° (c 0.21, MeOH); mp: 108-110°C; HRMS for C₃₄H₄₅N₆O₅ (M + H⁺) calculated 617.345144 found 617.343117.

3-(2-Phenyl-[1,3]dioxan-5-ylidene)-propan-1-ol (14). To suspension of 3-triphenylphosphoniumpropanol bromide (1.70 g, 4.24 mmol) in THF (20 mL) at –10°C, was added BuLi (3.56 mL, 1.5 M in hexanes), the resulting orange solution was stirred of 10 min. and TMSCl (0.54 mL, 4.24 mmol) was added. After stirring for an additional 5 min., a solution of **13** (0.755 g, 4.24 mmol) in THF (8 mL) was added dropwise and the resulting yellow solution was warmed up to room temperature over a periode of 3h. The reaction mixture was quenched with NH₄Cl (conc.), concentrated under vacuum, the aqueous solution was extracted with CH₂Cl₂, the combined organic extracts were washed with brine, dried over Na₂SO₄ and concentrated under vacuum. The resulting residue was dissolved in THF (10 mL), a solution of TBAF (4.24 mL, 1.0 M in THF) was added, the solution was stirred during 30 min. and concentrated under vacuum. The crude oil obtained was purified by flash chromatography (EtOAc/Hexanes 40:60) to give **14** (0.700 g, 75%) as a colourless oil; ¹H RMN (400 MHz, CDCl₃) δ 7.52-7.48 (m, 2H), 7.40-7.30 (m, 3H), 5.66 (s, 1H), 5.46 (t, 1H, J=7.5 Hz), 4.89 (d, 1H, J=12.8 Hz), 4.55 (d, 1H, J=12.8 Hz), 4.42 (t, 2H, J=12.8 Hz), 3.75-3.60 (m, 2H), 2.23-2.12 (m, 2H), 1.66 (t, 1H, J=5.6 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 138.5, 132.4, 129.4, 128.7, 126.5, 122.8, 102.0, 72.8, 66.7, 62.3, 30.6; HRMS for C₅H₁₇O₃ (M + H⁺) calculated 211.117770 found 221.117926.

5-(3-Azido-propylidene)-2-phenyl-[1,3]dioxane (15). To a solution of **14** (0.500 g, 2.27 mmol) in CH_2Cl_2 (18 mL), was added 2,4,6-collidine (0.60 mL, 4.5 mmol) followed by MsCl (0.35 mL, 4.5 mmol). After stirring for 2h, the solution was washed with a solution CuSO_4 (sat.), dried over Na_2SO_4 and concentrated under vacuum. To a solution of the residue obtained in DMF (15 mL), was added NaN_3 (1.48 g, 22.7 mmol), stirred at 50°C for 3h, concentrated under vacuum, the residue obtained was dissolved in EtOAc, the organic solution was washed with H_2O , brine, dried over Na_2SO_4 and concentrated under vacuum. The crude oil obtained was purified by flash chromatography (EtOAc/Hexanes 1:9) to give **15** (0.470 g, 85%) as a colourless oil; ^1H RMN (300 MHz, CDCl_3) δ 7.52-7.48 (m, 2H), 7.40-7.30 (m, 3H), 5.66 (s, 1H), 4.45 (t, 1H, $J=7.4$ Hz), 4.86 (d, 1H, $J=13.1$ Hz), 4.55 (d, 1H, $J=13.1$ Hz), 4.45-4.40 (m, 2H), 3.45-3.20 (m, 2H), 2.45-2.30 (m, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ 137.9, 132.2, 128.8, 128.2, 126.0, 121.5, 101.5, 72.1, 66.0, 50.6, 26.5; IR cm^{-1} 2833, 2360, 2097, 1453, 1259, 1118; HRMS for $\text{C}_{13}\text{H}_{16}\text{O}_2$ ($\text{M} + \text{H}^+$) calculated 246.124252 found 246.124416.

5-(3-Azido-propylidene)-2-tert-butoxycarbonylimino-dihydro-pyrimidine-1,3-dicarboxylic acid di-tert-butyl ester (16). The compound **15** (0.400 g, 1.63 mmol) was dissolved in AcOH (4 mL, 80% in H_2O) and stirred overnight. The solution was concentrated under vacuum, the residue was dissolved in EtOAc (8 mL), some NaHCO_3 was added to neutralize, the solution was filtrated, concentrated and purified by flash chromatography (EtOAc/Hexanes 60:40) to give the corresponding

diol (0.200 g, 78%) as a colourless oil; ^1H RMN (400 MHz, CDCl_3) δ 5.54 (t, 1H, $J=7.5$ Hz), 4.24 (s, 2H), 4.17 (s, 2H), 3.34 (t, 2H, $J=6.7$ Hz), 3.17 (broad s, 2H), 2.39 (q, 2H, $J=6.7$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 140.9, 126.0, 66.9, 59.5, 51.3, 27.6; IR cm^{-1} 3368, 2925, 2099. To a solution of the diol obtained (0.200 g, 1.27 mmol) and tris(Boc)guanidine (0.457 g, 1.27 mmol) in THF (25 mL) at 0°C , was added dropwise a ice-cooled solution of PPh_3 (0.700 g, 2.67 mmol) and DEAD (0.42 mL, 2.67 mmol) in THF (3.5 mL). After stirring for 30 min., NaHCO_3 (sat.) was added, the aqueous phase was extracted with CH_2Cl_2 , the combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The resulting residue was purified by flash chromatography (EtOAc/Hexanes 15:85) to give **16** (0.390 g, 64%) as a colourless oil; ^1H RMN (300 MHz, CDCl_3) δ 5.36 (t, 1H, $J=7.3$ Hz), 4.30 (s, 2H), 4.11 (s, 2H), 3.32 (t, 2H, $J=6.6$ Hz), 2.26 (q, 2H, $J=6.6$ Hz), 1.47 (s, 27H); ^{13}C NMR (75 MHz, CDCl_3) δ 157.9, 151.8, 151.0, 147.9, 134.3, 119.8, 83.4, 83.3, 79.6, 50.3, 48.4, 44.1, 28.0, 27.8, 27.4; IR cm^{-1} 2980, 2934, 2099, 1752, 1694, 1647, 1141; HRMS for $\text{C}_{22}\text{H}_{37}\text{N}_5\text{O}_6$ ($\text{M} + \text{H}^+$) calculated 481.277458 found 481.278862.

5-(3-Amino-propylidene)-2-*tert*-butoxycarbonylamino-5,6-dihydro-4H-pyrimidine-1-carboxylic acid *tert*-butyl ester (and its *N*-Boc regioisomer) (17**).**

To a solution of **16** (0.227 g, 0.472 mmol) in THF (6 mL), was added H_2O (4 drops) followed by PPh_3 (0.250 g, 0.945 mmol). After heating at 60°C for 3h, the solution was concentrated under vacuum, the residue was dissolved in Et_2O (10 mL), extracted with AcOH (10% in H_2O), the combined acidic extracts were washed with Et_2O , concentrated under vacuum and lyophilized. The fluffy white solid obtained was dissolved in H_2O , eluted on a Dowex 1X8-50 resin column (Cl^- form) and lyophilized to give **17** (0.108 g, 60%) as a fluffy white solid; ^1H RMN (400 MHz, CD_3OD) δ (mixture of regioisomers) 5.75 (broad m, 1H), 4.17 (s, 1H), 4.11 (s, 1H), 4.04 (s, 1H), 3.99 (s, 1H), 3.11 (t, 1H, $J=6.7$ Hz), 3.06 (t, 1H, $J=6.7$ Hz), 2.52 (q, 1H, $J=6.7$ Hz), 2.28 (q, 1H, $J=6.7$ Hz), 1.54 (s, 12H), 1.43 (s, 6H); ^{13}C NMR (100 MHz, CD_3OD) δ

(mixture of regioisomers) 157.5, 152.2, 151.5, 126.9, 125.5, 124.0, 123.4, 84.6, 84.5, 79.0, 45.2, 45.0, 40.7, 39.8, 39.5, 38.9, 28.6, 27.8, 27.1, 26.0; HRMS for $C_{17}H_{31}N_4O_4$ ($M + H^+$) calculated 355.234531 found 355.233486.

D-Pla(OMOM)-D-Phe-L-CHOI(OMOM)-2-[5-(3-Amino-propylidene)-2-*tert*-butoxycarbonylamino-5,6-dihydro-4H-pyrimidine-1-carboxylic acid *tert*-butyl ester] (and its *N*-Boc regioisomer) (10) (0.054 g, 0.093 mmol) in THF/H₂O (8 mL, 5:3), was added LiOH (0.010 g, 0.41 mmol) and the solution was stirred for 7h. The mixture was cooled down at 0°C, neutralized to pH=5 with HCl (2N), the aqueous phase was extracted with CH₂Cl₂, the combine organic extracts were washed with brine and dried over Na₂SO₄ to give the corresponding carboxylic acid as a white solid (0.050 g, quant.); ¹H RMN (400 MHz, CDCl₃) δ 7.40-7.05 (m, 10H), 5.05-4.95 (m, 1H), 4.68 (dd, 2H, *J*=6.6 Hz, *J*=14.3 Hz), 4.50 (d, 1H, *J*=6.8 Hz), 4.43 (d, 1H, *J*=6.8 Hz), 4.35-4.20 (m, 2H), 3.82 (s, 1H), 3.60-3.50 (m, 1H), 3.45 (s, 3H), 3.21-3.05 (m, 4H), 3.00-2.70 (m, 3H), 2.20-2.01 (m, 2H), 2.00 (m, 1H), 1.80-1.74 (m, 1H), 1.72-1.60 (m, 1H), 1.50-1.22 (m, 5H); ¹³C NMR (100 MHz, CDCl₃) δ 174.0, 171.4, 171.3, 137.4, 136.2, 130.2, 129.8, 129.0, 128.6, 127.6, 127.1, 96.6, 95.4, 78.3, 71.2, 59.4, 56.5, 56.0, 51.6, 40.3, 39.6, 35.9, 31.6, 29.4, 24.1, 19.7; [α]_D: -3.4° (c 1.25, CHCl₃); HRMS for $C_{31}H_{41}N_2O_8$ ($M + H^+$) calculated 569.286292 found 569.284400. To a solution of the acid obtained (0.043 g, 0.076 mmol), the amine **17** (0.037 g, 0.094 mmol) and ¹Pr₂NEt (42 μL, 0.30 mmol) in CH₂Cl₂ (3 mL) at 0°C, was added successively EDC (0.022 g, 0.11 mmol) and HOBt (0.016 g, 0.11 mmol), stirred at 0°C for 1h and overnight at RT. The solution was quenched with NaHCO₃ (sat.), the aqueous layer was extracted with CH₂Cl₂, the combined organic extracts were washed with brine and dried over Na₂SO₄. The solvent was removed under vacuum and the resulting oil was purified by flash chromatography (EtOAc/Hexanes 1:1 to 7:3) to give the corresponding pseudo tetrapeptide (0.047 g, 70 %) as a white solid;

^1H RMN (400 MHz, CDCl_3) δ (mixture of regioisomers) 9.60 (broad s, 1H), 7.30-7.10 (m, 10H), 6.07 (broad s, 0.5H), 5.50-5.38 (m, 1H), 5.08 (broad s, 0.5H), 5.00-4.80 (m, 1H), 4.78-4.59 (m, 4H), 4.56-4.37 (m, 2H), 4.28-4.20 (m, 1H), 4.19-4.10 (m, 1H), 4.08-3.95 (m, 1H), 3.92-3.80 (m, 2H), 3.78-3.60 (m, 1H), 3.56-3.30 (m, 4H), 3.20-3.02 (m, 4H), 3.00-2.80 (m, 4.5H), 2.58-2.25 (m, 1.5H), 2.23-2.18 (m, 1H), 2.17-2.02 (m, 2H), 2.00-1.91 (m, 1H), 1.90-1.72 (m, 3H), 1.70-1.08 (m, 20H); ^{13}C NMR (100 MHz, CDCl_3) δ (mixture of regioisomers) 174.8, 172.9, 170.9, 169.0, 165.4, 163.6, 159.2, 156.7, 137.6, 136.7, 130.2, 130.1, 129.8, 129.1, 128.9, 128.8, 128.6, 127.3, 127.0, 125.3, 96.9, 96.6, 96.5, 95.4, 79.3, 78.8, 78.3, 71.6, 71.5, 62.6, 56.7, 56.5, 56.0, 55.8, 51.5, 47.5, 42.2, 40.6, 40.0, 39.6, 36.8, 36.7, 32.6, 32.0, 31.4, 28.9, 28.8, 28.6, 24.5, 23.1, 19.9, 14.6, 14.5; $[\alpha]_D$: -62.1° (c 1.25, CHCl_3); HRMS for $\text{C}_{48}\text{H}_{69}\text{N}_6\text{O}_{11}$ ($\text{M} + \text{H}^+$) calculated 905.502433 found 905.504478.

Previously proposed Oscillarin (**2a**). To a solution of the pseudo tetrapeptide (0.033 g, 0.036 mmol) in THF (2 mL), was added HCl (1 mL, 12 N) and the solution was stirred at RT for 4h. The mixture was concentrated under vacuum and the residue purified by LC/MS (R_T =12 min., MeCN/ H_2O : 30% to 80% over 20 min. with 0.01% TFA, electrospray ionisation) on a semi-prep reverse phase column (C_{18} C-6000F Alltech, 250 X 22 mm) to give **2a** (0.014 g, 60%) as a fluffly white solid after freeze-drying; ^1H RMN (600 MHz, CD_3OD) δ 7.40-7.19 (m, 10H), 5.69 (t, 3/5H, J =7.4 Hz), 5.61 (t, 2/5H, J =7.4 Hz), 4.96-4.89 (m, 1H), 4.85-4.77 (m, 1H), 4.71 (d, 2/5H, J =15.4 Hz), 4.63 (d, 3/5H, J =15.4 Hz), 4.37 (d, 2/5H, J =16.0 Hz), 4.30-4.27 (m, 1H and 3/5H), 4.16 (dd, 1H, J =11.3 Hz, J =27.8 Hz), 4.05-3.95 (m, 2H), 3.80-3.72 (m, 1H), 3.07-3.02 (m, 3H), 2.90-2.80 (m, 2H), 2.78-2.76 (m, 1H), 2.50-2.44 (m, 2H), 2.22-2.18 (m, 1H), 2.15-2.10 (m, 1H), 2.00-1.73 (m, 4H), 1.57-1.41 (m, 3H); ^{13}C NMR (150 MHz, CD_3OD) δ 177.6,

174.7, 174.5, 174.2, 170.9, 170.6, 162.2, 162.0, 156.9, 156.7, 137.7, 136.1, 131.4, 130.4, 129.9, 129.5, 129.2, 128.8, 128.2, 127.4, 126.6, 123.1, 122.0, 97.5, 72.6, 65.4, 59.8, 59.7, 55.5, 51.6, 48.8, 44.8, 40.8, 39.6, 38.7, 37.4, 33.0, 31.9, 26.0, 25.8, 25.6, 18.8; $[\alpha]_D$: +79.4° (c 0.5, MeOH); mp: 112-116°C; HRMS for $C_{34}H_{45}N_6O_5$ ($M + H^+$) calculated 617.345144 found 617.345953.

(2S,4S)-4-But-3-enyl-5-oxo-pyrrolidine-1,2-dicarboxylic acid di-*tert*-butyl ester.

To a solution of the lactam (0.605 g, 3.07 mmol) in THF/H₂O (20 mL, 4:1), was added LiOH (0.294 g, 12.2 mmol) and the solution was stirred for 2h. The mixture was cooled to 0°C, acidified with HCl (2N) to pH=3, concentrated under vacuum, the acidic aqueous phase was extracted with CH₂Cl₂, the combined organic extracts were washed with brine, dried over Na₂SO₄ and concentrated under vacuum to give the corresponding acid (0.477 g, 85%); ¹H RMN (400 MHz, CDCl₃) δ 7.85 (broad s, 1H), 5.85-5.70 (m, 1H), 5.10-4.95 (m, 2H), 4.27 (t, 1H, J=7.9 Hz), 2.73-2.61 (m, 1H), 2.60-2.49 (m, 1H), 2.25-1.81 (m, 4H), 1.50-1.40 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 181.1, 174.5, 137.2, 115.5, 54.4, 41.0, 31.1, 30.9, 29.5; $[\alpha]_D$: +37.1° (c 1.1, CHCl₃); HRMS for C₉H₁₃NO₃ calculated 183.089543 found 183.088978. To a suspension of the acid obtained (0.400 g, 2.18 mmol) in *tert*-butyl acetate (3 mL), was added HClO₄ (70% in H₂O, 20 μL) and the solution was stirred for 24h. The mixture was quenched with NaHCO₃ (sat.), the organic phase was extracted with EtOAc, the combined organic extracts were washed with brine, dried over Na₂SO₄ and concentrated under vacuum. The crude oil obtained was purified by flash chromatography (EtOAc/Hexanes 1:1) to give the corresponding ester (0.470 g, 90%); ¹H RMN (400 MHz, CDCl₃) δ 6.58 (broad s, 1H), 5.83-5.70 (m, 1H), 5.05-4.90 (m, 2H), 4.05 (t, 1H, J=7.9 Hz), 2.61-2.45 (m, 1H), 2.42-2.25 (m, 1H), 2.20-1.88 (m, 3H), 1.80-1.68 (m, 1H), 1.50-1.38 (m, 10H); ¹³C NMR (100 MHz, CDCl₃) δ 179.4, 171.3, 138.1, 115.7, 82.7, 54.8, 40.9, 31.8, 31.7, 30.4, 28.3; $[\alpha]_D$: +12.7° (c 1.0, CHCl₃); electrospray MS for C₁₃H₂₁NO₃ calculated 239.2 found 239.2. To a solution of the *tert*-butyl ester lactam obtained (0.300 g, 1.25 mmol) in CH₂Cl₂ (6 mL), was added successively Et₃N

(0.52 mL, 3.76 mmol), Boc_2O (0.410 g, 1.88 mmol), DMAP (cat.) and the solution was stirred overnight. The mixture was quenched with NH_4Cl (2N), the aqueous phase was extracted with CH_2Cl_2 , the combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The crude oil obtained was purified by flash chromatography (EtOAc/Hexanes 15:85) to give the corresponding ester (0.380 g, 90%) as a colourless oil; ^1H RMN (400 MHz, CDCl_3) δ 5.80-5.65 (m, 1H), 5.05-4.90 (m, 2H), 4.38-4.32 (m, 1H), 2.55-2.35 (m, 2H), 2.20-1.90 (m, 3H), 1.65-1.30 (m, 20H); ^{13}C NMR (100 MHz, CDCl_3) δ 175.1, 170.3, 149.4, 137.1, 115.4, 83.1, 81.9, 57.9, 41.7, 30.9, 30.2, 27.7, 27.4; $[\alpha]_D$: -17.5° (c 0.72, CHCl_3); HRMS for $\text{C}_{18}\text{H}_{29}\text{NO}_5$ calculated 339.204573 found 339.205095.

(2S,3aS,6S,7aS)-6-Chloro-2,3,3a,4,5,6,7a-octahydroindole-1,2-dicarboxylic acid di-*tert*-butyl ester (18). Same procedure than compound 6 for reduction/acetylation (92%) and than compound 7 for cyclization (66%); ^1H RMN (400 MHz, CDCl_3) δ (mixture of rotamers) 4.20-4.02 (m, 1H), 4.00-3.88 (m, 0.6H), 3.82-3.64 (m, 1.4H), 2.62-2.57 (m, 0.6H), 2.53-2.43 (m, 0.4H), 2.33-2.20 (m, 1H), 2.18-2.07 (m, 1H), 2.03-1.60 (m, 6H), 1.50-1.37 (m, 18H); ^{13}C NMR (100 MHz, CDCl_3) δ (mixture of rotamers) 172.5, 172.2, 153.7, 153.6, 81.5, 80.4, 80.2, 60.6, 60.5, 57.7, 57.6, 56.9, 56.7, 38.6, 38.2, 35.9, 35.1, 32.9, 31.8, 31.7, 31.6, 28.8, 28.7, 28.4, 28.3, 25.1, 25.0; $[\alpha]_D$: -10.0° (c 0.8, CHCl_3); mp: 94-96°C; HRMS for $\text{C}_{18}\text{H}_{29}\text{ClNO}_4$ ($\text{M}-\text{H}^-$) calculated 360.192819 found 360.193000.

(2S,4R)-4-But-3-enyl-5-oxo-pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-methyl ester (21). To a solution of *N*-Boc pyroglutamic acid methyl ester 20 (1.51 g,

6.21 mmol) in THF (15 mL) at -78°C , was added LiHMDS (6.8 mL, 1.0 N in THF), stirred for 30 min. and a solution of 3-butenol-O-Tf prepared (2.54 g, 12.4 mmol) in THF (15 mL) at -78°C was added dropwise *via canula*. After stirring for 1h, the solution was quenched with NH_4Cl (2N), warmed up to RT, concentrated under vacuum. The resulting aqueous solution was extracted with CH_2Cl_2 , the combined organic extracts were washed with brine and dried over Na_2SO_4 . The solvent was removed under vacuum and the resulting oil was purified by flash chromatography (EtOAc/Hexanes 1:9 to 15:85) to give the *syn* compound **5** (0.833 g, 45%) and the *anti* compound **21** (0.460 g, 25%) as colourless oils; ^1H RMN (400 MHz, CDCl_3) δ 5.80-5.69 (m, 1H), 5.05-4.92 (m, 2H), 4.55 (dd, 1H, $J=1.3$ Hz, $J=8.2$ Hz), 3.76 (s, 3H), 2.63-2.56 (m, 1H), 2.25-1.90 (m, 5H), 1.52-1.35 (m, 11H); ^{13}C NMR (100 MHz, CDCl_3) δ 175.4, 172.2, 149.9, 137.7, 115.9, 83.9, 57.4, 52.9, 41.4, 31.3, 30.0, 28.9, 28.3; $[\alpha]_D$: -2.0° (c 0.95, CHCl_3); HRMS for $\text{C}_{15}\text{H}_{25}\text{NO}_5$ ($\text{M} + \text{H}^+$) calculated 298.16544 found 298.16448.

(2S,3aR,6R,7aR)-6-Chloro-2,3,3a,4,5,6,7,7a-octahydroindole-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester (23). To a solution of **21** (0.120 g, 0.400 mmol) in THF (4 mL) at -78°C , was added a solution of LiHBEt_3 (0.44 mL, 1.0 N in THF), stirred for 1h, quenched with NaHCO_3 (sat.) and 2 drops of H_2O_2 (30% in H_2O) and concentrated under vacuum. The resulting oil was dissolved in CH_2Cl_2 (3 mL) and Et_3N (0.17 mL, 1.21 mmol), Ac_2O (0.11 mL, 1.21 mmol) and DMAP (cat.) were added successively. After stirring overnight, the solution was quenched with NaHCO_3 (sat.), the aqueous layer was extracted with CH_2Cl_2 , the combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The crude oil obtained was purified by flash chromatography (EtOAc/Hexanes 15:85) to give the corresponding hemiaminal derivative **22** as a mixture of diastereoisomers. To a solution of the unstable hemiaminal derivative in CH_2Cl_2 (3 mL) at -78°C was added a solution of SnCl_4 (0.46 mL, 1.0 M in CH_2Cl_2) dropwise. After stirring for 10

min., the solution was quenched with NaHCO_3 (sat.), warmed up to RT, filtered on a small celite pad, the filtrate was washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The crude oil obtained was purified by flash chromatography (EtOAc/Hexanes 1:9 to 15:85) to give **23** (0.071 g, 64%) as a colourless oil; ^1H RMN (400 MHz, CDCl_3) δ (mixture of rotamers) 4.32 (d, 0.5H, $J=9.3$ Hz), 4.25 (d, 0.5H, $J=9.3$ Hz), 4.12-3.95 (m, 0.5H), 3.92-3.85 (m, 0.5H), 3.70 (s, 4H), 2.75-2.70 (m, 0.5H), 2.61-2.40 (m, 1.5H), 2.25-2.20 (m, 1H), 2.05-1.97 (m, 1H), 1.82-1.58 (m, 4H), 1.50-1.35 (m, 10H); ^{13}C NMR (100 MHz, CDCl_3) δ (mixture of rotamers) 173.8, 173.5, 154.0, 153.4, 80.7, 80.5, 58.8, 58.4, 57.1, 56.9, 56.7, 56.5, 52.6, 52.4, 39.4, 38.7, 34.3, 33.4, 32.3, 31.9, 31.7, 31.2, 28.8, 28.6, 24.8, 24.7; $[\alpha]_D^{25}$: -9.3° (c 1.16, CHCl_3); HRMS for $\text{C}_{15}\text{H}_{25}\text{NO}_4\text{Cl}$ ($M + \text{H}^+$) calculated 317.139386 found 317.138748.

(2S,4S)-3-But-3-enyl-5-hydroxymethyl-pyrrolidin-2-one. To an ice cooled solution of **24** (0.484 g, 2.45 mmol) in EtOH (5 mL), was added NaBH_4 (0.140 g, 3.68 mmol), stirred for 30 min. at 0°C and 1h at RT. The solution was cooled down to 0°C , quenched with HCl (2N) to pH=3, the solution was extracted with CH_2Cl_2 , the combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The crude oil obtained was purified by flash chromatography ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 9:1) to give the corresponding alcohol (0.361 g, 87%) as a colourless oil; ^1H RMN (400 MHz, CDCl_3) δ 7.46 (broad s, 1H), 5.80-5.70 (m, 1H), 5.04-4.92 (m, 2H), 4.77 (broad s, 1H), 3.75-3.60 (m, 2H), 3.22-3.15 (m, 1H), 2.23-2.17 (m, 1H), 2.15-2.10 (m, 1H), 2.08-1.90 (m, 3H), 1.20-1.12 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 180.8, 138.1, 115.7, 66.4, 55.4, 41.4, 31.8, 30.6, 29.9; $[\alpha]_D^{25}$: $+82.3^\circ$ (c 0.56, CHCl_3); HRMS for $\text{C}_9\text{H}_{15}\text{NO}_2$ calculated 169.110279 found 169.110431.

(2R,4S)-3-But-3-enyl-5-methyl-2-oxo-pyrrolidine-1-carboxylic acid tert-butyl ester (25). To an ice cooled solution of the alcohol (0.230 g, 1.36 mmol), cyclohexene (0.27 mL, 0.272 mmol) and PPh_3 (0.534 g, 0.204 mmol) in MeCN (5 mL), was added a solution of CBr_4 (0.676 g, 0.272 mmol) in MeCN (1 mL) and the mixture was warmed to RT. After stirring overnight, the solution was quenched with H_2O , concentrated under vacuum, the residue was dissolved in $\text{H}_2\text{O}/\text{CH}_2\text{Cl}_2$, the aqueous phase was extracted with CH_2Cl_2 , the combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The crude oil obtained was purified by flash chromatography (EtOAc/Hexanes 75:25). To a solution of the bromide obtained (0.600 g, 2.58 mmol) in toluene (14 mL), was added Bu_3SnH (0.83 mL, 3.10 mmol) followed by AIBN (0.004 g, 0.03 mmol) and heated at 80°C for 5h. The solution was then concentrated under vacuum and the crude oil was purified by flash chromatography ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 10:1). To a solution of the dehalogenated product obtained in CH_2Cl_2 (10 mL), was added successively Et_3N (1.08 mL, 7.75 mmol), Boc_2O (0.846 g, 3.88 mmol), DMAP (cat.) and the solution was stirred overnight. The mixture was quenched with NH_4Cl (2N), the aqueous phase was extracted with CH_2Cl_2 , the combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The crude oil obtained was purified by flash chromatography (EtOAc/Hexanes 15:85) to give **25** as a colourless oil (0.229 g, 35% for 3 steps); ^1H RMN (400 MHz, CDCl_3) δ 5.80-5.35 (m, 1H), 5.05-4.95 (m, 2H), 4.02-3.95 (m, 1H), 2.45-2.25 (m, 2H), 2.20-1.96 (m, 4H), 1.47 (s, 9H), 1.45-1.38 (m, 1H), 1.35 (d, 3H, $J=6.1$ Hz), 1.15-1.08 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 176.8, 150.8, 138.0, 115.8, 83.1, 52.6, 42.4, 32.8, 31.7, 31.0, 28.4, 22.5; $[\alpha]_D$: -33.2° (c 1.15, CHCl_3); HRMS for $\text{C}_{14}\text{H}_{25}\text{NO}_3$ ($M + \text{H}^+$) calculated 254.175619 found 254.176400.

(2R,3aS,6S,7aS)-6-Chloro-2-methyl-2,3,3a,4,5,6,7,7a-octahydroindole-1-carboxylic acid *tert*-butyl ester (27). Same procedure than compound **6** for reduction/acetylation (80%) and than compound **7** for cyclization (60%); ¹H RMN (400 MHz, DMSO-d₆) δ 4.00-3.90 (m, 1H), 3.85-3.70 (m, 1H), 3.67-3.58 (m, 1H), 3.50 (s, 3H), 2.35-2.22 (m, 1H), 2.17-2.03 (m, 1H), 1.98-1.81 (m, 2H), 1.75-1.57 (m, 2H), 1.40 (broad s, 9H), 1.22 (broad m, 3H); ¹³C NMR (100 MHz, DMSO-d₆) δ (mixture of rotamers) 79.9, 79.7, 58.5, 58.2, 56.4, 54.1, 53.9, 40.5, 40.1, 36.1, 35.5, 35.1, 34.8, 31.7, 27.8, 24.7, 22.2, 21.2; [α]_D: +79.4° (c 0.5, CHCl₃); HRMS for C₁₄H₂₄ClNO₂ calculated 273.149557 found 273.149750.

(2S)-5-But-3-enyl-6-oxo-piperidine-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-methyl ester (29). To a solution of the lactam (0.500 g, 1.94 mmol) in THF (5 mL) at -78°C , was added a solution of LiHMDS (2.1 mL, 1.0 M in THF). After stirring for 20 min., a solution of 3-butenol-*O*-Tf (0.730 g, 3.60 mmol) in THF (5 mL) at -78°C was transferred *via canula*. The solution was stirred for 5h, quenched with NH_4Cl (2N), warmed to RT, concentrated under vacuum, the residue was dissolved in $\text{H}_2\text{O}/\text{CH}_2\text{Cl}_2$, the aqueous phase was extracted with CH_2Cl_2 , the combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The crude oil obtained was purified by flash chromatography ($\text{EtOAc}/\text{Hexanes}$ 1:9) to give 29 as an inseparable mixture of diastereoisomers (0.585 g, 90%, 1.3:1 *anti/syn*).

To a solution of **29** (0.500 g, 1.61 mmol) in CH_2Cl_2 (10 mL), was added TFA (0.60 mL, 8.05 mmol). After stirring for 1h, the solution was neutralized with NaHCO_3 (sat.), the aqueous phase was extracted with CH_2Cl_2 , the combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The crude oil obtained was purified by flash chromatography (EtOAc/Hexanes 8:2) to give the corresponding lactams *anti* (0.170 g, 50%) and *syn* (0.130 g, 38%) as colourless oils; **(2S,5R)-5-But-3-enyl-6-oxo-piperidine-2-carboxylic acid methyl ester (*anti*)**; ^1H RMN (400 MHz, CDCl_3) δ 6.30-6.22 (broad s, 1H), 5.83-5.70 (m, 1H), 5.05-4.90 (m, 2H), 4.06 (dd, 1H, $J=4.7$ Hz, $J=10.3$ Hz), 3.76 (s, 3H), 2.30-1.96 (m, 6H), 1.78-1.62 (m, 1H), 1.58-1.40 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 174.2, 171.9, 138.4, 115.5, 55.2, 53.1, 40.4, 31.3, 30.8, 25.8, 25.6; $[\alpha]_D$: -30.1° (c 0.50, CHCl_3); HRMS for $\text{C}_{11}\text{H}_{18}\text{NO}_3$ ($\text{M}+\text{H}^+$) calculated 212.128669 found 212.129400; **(2S,5S)-5-But-3-enyl-6-oxo-piperidine-2-carboxylic acid methyl ester (*syn*)**; ^1H RMN (400 MHz, CDCl_3) δ 6.43-6.38 (broad s, 1H), 5.82-5.70 (m, 1H), 5.02-4.90 (m, 2H), 4.10-4.05 (m, 1H), 3.75 (s, 3H), 2.37-2.20 (m, 1H), 2.18-2.10 (m, 1H), 2.09-1.90 (m, 4H), 1.94-1.80 (m, 1H), 1.58-1.42 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 174.8, 172.5, 138.4, 115.5, 54.8, 53.0, 40.2, 31.4, 30.8, 24.3, 24.0; $[\alpha]_D$: $+36.8^\circ$ (c 0.73, CHCl_3); HRMS for $\text{C}_{11}\text{H}_{18}\text{NO}_3$ ($\text{M}+\text{H}^+$) calculated 212.128669 found 212.129326.

(2S,5R)-5-But-3-enyl-6-oxo-piperidine-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-methyl ester (31). To a solution of the lactam *anti* (0.170 g, 0.804 mmol) in CH_2Cl_2 (8 mL), was added successively Et_3N (0.34 mL, 2.41 mmol), Boc_2O (0.263 g, 1.21 mmol), DMAP (cat.) and the solution was stirred overnight. The mixture was quenched with NH_4Cl (2N), the aqueous phase was extracted with CH_2Cl_2 , the

combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The crude oil obtained was purified by flash chromatography (EtOAc/Hexanes 2:8) to give **31** (0.225 g, 90%) as a colourless oil; ^1H RMN (400 MHz, CDCl_3) δ 5.82-5.70 (m, 1H), 5.10-4.90 (m, 2H), 4.70 (t, 1H, $J=5.9$ Hz), 3.75 (s, 3H), 2.48-2.37 (m, 1H), 2.12-1.84 (m, 6H), 1.60-1.40 (m, 12H); ^{13}C NMR (100 MHz, CDCl_3) δ 173.9, 172.5, 153.0, 138.2, 115.7, 83.9, 58.7, 53.0, 42.9, 31.5, 31.0, 28.3, 28.0, 24.1, 24.0; $[\alpha]_D$: -32.9° (c 0.68, CHCl_3); HRMS for $\text{C}_{16}\text{H}_{27}\text{NO}_5$ ($\text{M}+\text{H}^+$) calculated 312.181098 found 312.180600.

(2S,5S)-5-But-3-enyl-6-oxo-piperidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester (30). Same procedure than compound **31**. (0.170 g, 90%); ^1H RMN (400 MHz, CDCl_3) δ 5.85-5.70 (m, 1H), 5.05-4.90 (m, 2H), 4.70-4.60 (m, 1H), 3.75 (s, 3H), 2.43-2.37 (m, 1H), 2.25-1.97 (m, 5H), 1.95-1.80 (m, 1H), 1.60-1.40 (m, 12H); ^{13}C NMR (100 MHz, CDCl_3) δ 173.5, 172.6, 153.3, 138.4, 115.5, 83.2, 59.2, 52.9, 43.8, 31.0, 30.7, 28.3, 25.8, 24.4; $[\alpha]_D$: $+29.5^\circ$ (c 0.75, CHCl_3); HRMS for $\text{C}_{16}\text{H}_{27}\text{NO}_5$ ($\text{M}+\text{H}^+$) calculated 312.181098 found 312.180652.

(2S,4aR,7S,9aS)-7-Chloro-2,3,4,4a,5,6,7,8,9,9a-dodecahydroquinoline-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester (34). Same procedure than compound **6** for reduction/acetylation (75%) and than compound **7** for cyclization (63%); ^1H RMN (400 MHz, CDCl_3) δ (mixture of rotamers) 4.85-4.80 (m, 0.4H), 4.67-4.61 (m, 0.6H), 4.18-4.10 (m, 0.6H), 4.05-3.97 (m, 0.4H), 3.80-3.60 (m, 4H), 2.45-2.32 (m, 1H), 2.30-2.22 (m, 0.6H), 2.21-2.12 (m, 0.4H), 1.95-1.87 (m, 1H), 1.80-1.25

(m, 17H); ^{13}C NMR (100 MHz, CDCl_3) δ (mixture of rotamers) 173.1, 173.0, 155.0, 154.8, 80.3, 80.2, 57.5, 52.9, 52.0, 51.9, 51.7, 50.9, 36.6, 35.7, 33.6, 33.5, 31.5, 31.4, 29.8, 28.2, 28.1, 25.8, 25.7, 20.6, 20.5; $[\alpha]_D$: -9.5° (c 0.55, CHCl_3); mp: 115-118 $^\circ\text{C}$; HRMS for $\text{C}_{16}\text{H}_{27}\text{ClNO}_4$ ($\text{M}+\text{H}^+$) calculated 332.162861 found 332.163800.

(2S,4aR,7R,9aS)-7-Chloro-2,3,4,4a,5,6,7,8,9,9a-dodecahydroquinoline-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester (35). (8%); ^1H RMN (400 MHz, CDCl_3) δ 4.83-4.72 (m, 1H), 4.65-4.57 (m, 1H), 4.52-4.48 (m, 1H), 3.68 (s, 3H), 2.40-2.30 (m, 1H), 2.28-2.13 (m, 1H), 2.10-1.80 (m, 4H), 1.78-1.37 (m, 12H), 1.36-2.22 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 174.1, 80.6, 60.3, 57.3, 52.5, 52.0, 35.2, 31.4, 29.5, 28.7, 28.4, 26.6, 25.7, 21.3; $[\alpha]_D$: -80.6° (c 0.30, CHCl_3); mp: 93-96 $^\circ\text{C}$; HRMS for $\text{C}_{16}\text{H}_{27}\text{ClNO}_4$ ($\text{M}+\text{H}^+$) calculated 332.162861 found 332.163786.

(2S,4aS,7R,9aR)-7-Chloro-2,3,4,4a,5,6,7,8,9,9a-dodecahydroquinoline-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester (37). Same procedure than compound 6 for reduction/acetylation (84%) and than compound 7 for cyclization (35%); ^1H RMN (400 MHz, CDCl_3) δ (mixture of rotamers) 4.20-4.15 (m, 0.5H), 4.13-4.07 (m, 0.5H), 4.05 (m, 0.5H), 3.94-3.63 (m, 4.5H), 2.40-2.30 (m, 0.5H), 2.23-1.17 (m, 0.5H), 2.15-1.90 (m, 4H), 1.75-1.52 (m, 5H), 1.50-1.35 (m, 10H); ^{13}C NMR (100 MHz, CDCl_3) δ 174.2, 173.9, 156.0, 155.3, 81.1, 57.7, 54.1, 54.0, 53.7, 52.9, 52.6, 52.4, 38.6, 38.2, 31.4, 30.9, 30.0, 29.5, 28.7, 28.6, 26.2, 25.4, 20.3, 19.6; $[\alpha]_D$: -74.3° (c 1.0, CHCl_3); HRMS for $\text{C}_{16}\text{H}_{27}\text{ClNO}_4$ ($\text{M}+\text{H}^+$) calculated 332.162861 found 332.163802.

(2S,4aS,7S,9aR)-7-Chloro-2,3,4,4a,5,6,7,8,9,9a-dodecahydroquinoline-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester 38. (3%); ^1H RMN (300 MHz, CDCl_3) δ 4.65-4.42 (m, 2H), 4.15-3.95 (m, 1H), 3.72 (s, 3H), 2.24-1.68 (m, 8H), 1.65-1.38 (m, 12H); ^{13}C NMR (100 MHz, CDCl_3) δ 173.4, 155.2, 80.4, 59.1, 53.4, 52.0, 48.7, 33.6, 31.5, 28.1, 27.6, 26.1, 24.4, 19.9; $[\alpha]_D$: +11.8° (c 0.30, CHCl_3), mp: 125-127°C; HRMS for $\text{C}_{16}\text{H}_{27}\text{ClNO}_4$ ($\text{M}+\text{H}^+$) calculated 332.162861 found 332.163773.

(2S,4aR,7S,9aS)-7-Bromo-2,3,4,4a,5,6,7,8,9,9a-dodecahydroquinoline-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester (36). Same procedure than compound 6 for reduction/acetylation (75%) and than compound 7 for cyclization (65%); ^1H RMN (400 MHz, CDCl_3) δ (mixture of rotamers) 4.84-4.82 (d, 0.4H, $J=5.0$ Hz), 4.65-4.63 (d, 0.6H, $J=5.0$ Hz), 4.15-4.08 (m, 0.6H), 4.02-3.95 (m, 0.4H), 3.92-3.78 (m, 1H), 3.71 (s, 3H), 2.40-2.20 (m, 2H), 2.07-1.97 (m, 1H), 1.83-1.55 (m, 7H), 1.48 (s, 3.6H), 1.42 (s, 5.4H), 1.38-1.20 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ (mixture of rotamers) 173.7, 173.5, 155.5, 155.3, 80.9, 80.8, 54.0, 52.8, 52.6, 52.5, 51.5, 49.4, 49.3, 38.0, 37.1, 34.2, 34.0, 32.8, 32.7, 31.4, 28.8, 28.7, 26.3, 26.2, 21.2, 21.0; $[\alpha]_D$: +7.9° (c 0.86, CHCl_3); HRMS for $\text{C}_{16}\text{H}_{27}\text{BrNO}_4$ ($\text{M}+\text{H}^+$) calculated 376.112345 found 376.111300.

(2S,4aS,7R,9aR)-7-Bromo-2,3,4,4a,5,6,7,8,9,9a-dodecahydroquinoline-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester (39). Same procedure than compound **6** for reduction/acetylation (84%) and than compound **7** for cyclization (31%); ^1H RMN (400 MHz, CDCl_3) δ (mixture of rotamers) 4.21-4.08 (m, 1H), 4.07-3.83 (m, 2H), 3.72 (s, 3H), 2.52-2.41 (m, 0.5H), 2.38-2.28 (m, 0.5H), 2.20-1.90 (m, 4H), 1.89-1.70 (m, 2H), 1.68-1.30 (m, 13H); ^{13}C NMR (100 MHz, CDCl_3) δ (mixture of rotamers) 175.0, 155.0, 81.2, 54.5, 54.1, 53.7, 53.4, 52.5, 48.6, 39.5, 39.2, 32.3, 30.8, 30.6, 30.0, 28.7, 28.6, 26.2, 25.3, 20.3, 19.6; $[\alpha]_D$: -48.0° (c 0.75, CHCl_3); HRMS for $\text{C}_{16}\text{H}_{27}\text{BrNO}_4$ ($\text{M}+\text{H}^+$) calculated 376.112345 found 376.111287.

Complex α -Thrombin/Oscillarin

The complex of human α -Thrombin and hirugen was prepared as previously reported (1). Crystals of the complex were prepared using the hanging drop vapor diffusion technique using 27 % V/V PEG8000 buffered at pH 7.3 using 50 mM Na Phosphate. Human α -Thrombin was purchased from Enzyme Research Laboratories Inc., South Bend, IN, and hirugen from American Diagnostica Inc, Greenwich, CT. The X-ray diffraction data were collected at 100 K on a MAR DTB imaging plate system using Cu K α radiation from a rotating anode. The data were reduced and scaled using the program Mosfilm and the programs SCALA and TRUNCATE from the CCP4 program package (2). The structure of human α -Thrombin-hirugen complex previously examined in our lab was used in the refinement of the Oscillarin/ α -Thrombin/Hirugen complex structure. The refinement was performed using the program CNX (3). Statistics from the data-collection and refinement is included in table 1. The atomic coordinates of the complex have been deposited to the PDB (entry code 1RIW).

Table 1. Parameters and Statistics for X-ray crystallography. Data-collection and refinement.	
No. of measurements	69514
No. of unique reflections	22273
Completeness (%)	98.8
R _{sym} ^a (%)	6.7
No. of atoms in protein model.	2388
No of solvent molecules.	217
Resolution range used for refinement. (Å)	24.68-2.04
r.m.s.d. from ideal values ,bond length (Å)	0.006
r.m.s d. from ideal values bond angles (°)	1.4
R _{work} ^b (%)	21.3
R _{free} ^b (%)	23.2

$$^a R_{sym} = \frac{\sum_{hkl} \sum_i |I(h,k,l,i) - \langle I(h,k,l) \rangle|}{\sum_{hkl} \sum_i I(h,k,l,i)}$$

and where $\langle I(h,k,l) \rangle$ represents the average intensity

of symmetry equivalent reflections.

$$^b R_{work} \text{ and } R_{free} \text{ are calculated as: } R = \frac{\sum_{hkl} |F_{obs}(h,k,l)| - |F_{calc}(h,k,l)|}{\sum_{hkl} |F_{obs}(h,k,l)|}$$

. |F_{obs}| is the

observed amplitude of the structure factor and |F_{calc}| is the calculated amplitude of the structure factor. R_{free} is calculated from 5 % of the reflections that have been omitted from the refinement. R_{work} is calculated using all data except the reflections that have been included in the test set.

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S33

28.192
28.246
30.497
31.482

42.205

52.893

57.784

77.172
77.490
77.808
84.045

116.148

137.622

149.0

172.396

175.423

ppm

S38