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The First Total Synthesis of Efrapeptin C

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Abbreviations

Azib: α-azidoisobutyryl; **DBN**: 1,4-diazabicyclo[4.3.0]non-5-ene; **DBU**: 1,8-diazabicyclo[5.4.0]undec-7-ene; **DMAP**: 4-dimethylaminopyridine; **DIPEA**: *N*,*N*'-Diisopropylethylamine; **TBME:** *tert*-butylmethylether; **N-HATU**: 1-[Bis-(dimethylamino)methyliumyl]-1*H*-1,2,3-triazolo[4,5-*b*]pyridine-3-oxide hexafluorophosphate; **PyBOP**: 1-benzotriazolyloxy-tris-pyrrolidinophosphonium hexafluorophosphate; **TBTU**: 1-[Bis(dimethylamino)methyliumyl]-1*H*-benzotriazole-3-oxide tetrafluoroborate .

General

Unless otherwise noted, materials were obtained from commercial suppliers and were used without further purification. DMF was distilled at 55 mbar over ninhydrine, dichloromethane was distilled first over calcium chloride and subsequently dried over calcium hydride. α-Azidoisobutyric acid (Azib-OH) was synthesized starting from α-bromoisobutyric acid ethyl ester following known procedures.[1] Azib-OH was treated with thionyl chloride to give the acid chloride, which was purified by distillation under reduced pressure (bp.: 45°C/20 mbar). Tin(II)thiophenolate was obtained from the reaction of KOH and thiophenol with $SnCl_2$ in ethanol. For thin-layer chromatography (TLC) silica gel plates Merck 60 F_{254} were used; compounds were visualized by irradiation with UV light and/or by treatment with a solution of ninhydrine in ethanol followed by heating. Flash chromatography was performed using silica gel Merck 60 (particle size 0.040-0.063 mm). Preparative RP-HPLC was carried out using a Thermo Separation Products system consisting of a UV1000 detector and a P4000 pump equipped with a Vydac high performance guard column (protein and peptide C18) and a Vydac 218TP1022 efficiency protein and peptide C18 column (22 x 250 mm, Eluents: A = H_2O/CH_3CN/TFA (95/5/0.1), B = H_2O/CH_3CN/TFA (5/95/0.1); method A: flow rate: 10 mL/min, gradient (A:B): 0-5 min: 100:0 , 5-30 min: 100:0-70:30, 30-40 min 70:30-0:100, method B: flow rate: 15 mL/min, gradient (A:B): 0-5 min: 100:0 , 5-30 min: 100:0-40:60, 30-40 min 40:60-0:100, method C: flow rate: 15 mL/min, gradient (A:B): 0-3 min: 100:0 , 3-30 min: 100:0-40:60, 30-40 min 40:60-0:100. Fractions containing the desired products were identified by MALDI-ToF MS and combined. The purity of the products was checked by analytical RP-HPLC. Analytical RP-HPLC was carried out using a Thermo Separation

Products system consisting of a UV6000 detector and a P4000 pump equipped with a Vydac high performance guard column (protein and peptide C18) and a Vydac 218TP54 efficiency protein and peptide C18 column (4.6 x 250 mm, Eluents: A = H_2O/CH_3CN/TFA (95/5/0.1), B = H_2O/CH_3CN/TFA (5/95/0.1); method A: flow rate: 1 mL/min, gradient (A:B): 0-5 min: 100:0, 5-30 min: 100:0-70:30, 30-40 min 70:30-0:100, method B: flow rate: 1 mL/min, gradient (A:B): 0-3 min: 100:0 , 3-30 min: 100:0-40:60, 30-40 min 40:60-0:100; method C: flow rate: 1 mL/min, gradient (A:B): 0-5 min: 100:0 , 5-30 min: 100:0-40:60, 30-40 min 40:60-0:100. ^{1}H NMR and ^{13}C NMR spectra were recorded at room temperature on a Bruker DRX 500 instrument. Chemical shifts are given in ppm relative to TMS as internal standard. Infrared spectra (IR) were recorded on a Jasco FT/IR-410 spectrometer; peaks are reported as wavenumbers in cm^{-1}. MALDI-ToF mass spectra were recorded on a Voyager-DE instrument (PerSeptive Biosystems) with 2,5-dihydroxybenzoic acid as the matrix and were calibrated with a PEG standard as external reference. Electrospray ionization (ESI) mass spectrometry experiments were performed on a Bruker Esquire 3000 spectrometer. ESI-FT-ICR mass spectrometry experiments were performed on a Bruker Apex III spectrometer with internal calibration. Chemical Ionization (CI) mass spectrometry experiments were performed on a Micromass VG Autospec X spectrometer. Melting points were recorded on a Büchi melting point B-540 apparatus and are uncorrected.

Solid Phase Peptide Synthesis

In solid phase peptide synthesis Aib residues were introduced as described in the text and all other amino acids were introduced as Fmoc-amino acids. The Fmoc-amino acid (3 equiv) and the coupling reagent (TBTU or PyBOP in the case of pipecolic acid) were dissolved in DMF and DIPEA (3 equiv) was added. The solution was mixed for 30 sec. and added to the peptidyl resin preswollen in DMF. After the addition of a further amount of DIPEA (3 equiv), the mixture was left for 50 min and agitated occasionally. If the starting material was still detected by MALDI-ToF MS analysis after 50 min using a small sample cleaved from the resin, the reaction time was increased. The Fmoc group was removed by twofold treatment with 2% DBU and 2% piperidine in DMF for 15 min. The crude product was cleaved from the resin by treatment with 1% TFA in dichloromethane for 1 h.

Preparation of 1

DIPEA (5.8 µL, 33.2 µmol, 3.3 equiv) was added at 0°C to a stirred solution of Ac-Pip-Aib-Pip-Aib-Aib-Leu-ß-Ala-Gly-OH **10** (10.3 mg, 13.2 µmol, 1.3 equiv) and N-HATU (5.0 mg, 13.2 µmol, 1.3 equiv) in DMF (0.6 mL). After 10 min amidinium salt **11** (11.1 mg, 10.3 µmol, 1.0 equiv) dissolved in dry dichloromethane (1.2 mL) was added and the reaction mixture was left overnight at 0°C. The reaction was monitored by MALDI-ToF-MS. The volatiles were removed in vacuo and the product was isolated by RP-HPLC (method C). Yield: 11.9 mg (6.9 µmol, 67%)

Analytical data for **1**: Analytical HPLC (method B): t_R = 32.75 min. ^{1}H NMR (500 MHz, CD_2Cl_2, TMS): δ = 0.86 (d, J = 6.2 Hz, 3H), 0.87 (d, J = 6.7 Hz, 3H), 0.89 (d, J = 6.7 Hz, 3H), 0.92 (d, J = 6.5 Hz, 3H), 0.94 (d, J = 7.2 Hz, 3H), 0.95 (d, J = 7.0 Hz, 3H), 1.19 (ddd, J = 3.6 Hz, J = 10.0 Hz, J = 13.6 Hz, 1H), 1.25-1.32 (m, 2H), 1.40-2.14 (m, 27H), 1.44 (s, 3H), 1.46 (s, 6H), 1.47 (s, 3H), 1.48 (s, 3H), 1.50 (s, 3H), 1.51-1.52 (m, 12H), 1.53 (s, 3H), 1.55 (s, 6H), 1.58 (s, 3H), 2.17 (s, 3H), 2.26-2.38 (m, 2H), 2.73 (m, 1H), 2.79 (m, 1H), 3.01-3.11 (m, 2H), 3.20-3.44 (m, 7H), 3.54-3.72 (m, 5H), 3.76-3.83 (m, 3H), 3.89-3.97 (m, 2H), 3.98-4.08 (m, 2H), 4.12 (ddd, J = 3.8 Hz, J = 7.2 Hz, J = 11.1 Hz, 1H), 4.26 (m, 1H), 4.36 (m, 1H), 4.49 (m, 1H), 4.80 (m, 1H), 5.20 (m, 1H), 6.75 (d, J = 9.4 Hz, 1H), 7.29 (s, 1H), 7.15 (s, 1H), 7.38 (m, 1H), 7.47 (s, 1H), 7.52 (d, J = 7.4 Hz, 1H), 7.61 (s, 1H), 7.65 (t, J = 4.5 Hz, 1H), 7.77 (s, 1H), 7.84 (s, 1H), 8.01 (s, 1H), 8.04 (s, 1H), 8.07 (d, J = 5.1 Hz, 1H). MS (ESI-FT-ICR): *m/z* : found 1606.0444, monoisotopic mass calculated for the cation $C_{80}H_{137}N_{18}O_{16}^+$: 1606.0454.

Preparation of Boc-Leu-Aib-OAll 4:

Hydrogen chloride was passed through a suspension of α-aminoisobutyric acid **2** (10.00 g, 97.0 mmol) in allyl alcohol (200 mL) for 30 min. The solution was heated to 90°C overnight. Excess allyl alcohol was removed by rotary evaporation, the residue was treated with saturated aqueous sodium carbonate (100 mL) and dichloromethane (100 mL) and stirred vigorously for 30 min. The organic phase was separated, dried over sodium sulfate and concentrated in vacuo. The crude product was purified by distillation (Bp.: 67°C/50 mbar). Yield: 9.94 g (69.4 mmol, 72%)

α-Aminoisobutyric acid allyl ester **3** (0.644 g, 4.50 mmol, 1.0 equiv) was added under argon at 0°C to a solution prepared by dissolving Boc-Leu-OH (1.143 g, 4.94 mmol, 1.1 equiv),

PyBOP (2.570 g, 4.94 mmol, 1.1 equiv) and DIPEA (1.650 mL, 9.45 mmol, 2.1 equiv) in dry dichloromethane (6 mL). The mixture was stirred for 5 min at 0°C and 1 h at room temperature. The solvent was removed by rotary evaporation and the residue dissolved in ethyl acetate (70 mL). The solution was washed with 5% aqueous $KHSO_4$, 5% aqueous $NaHCO_3$, dried over sodium sulfate and concentrated in vacuo. The product was isolated by flash chromatography (silica gel, petrol ether/ethyl acetate 7:3) as a colourless solid. Yield: 1.277 g (3.58 mmol, 80%).

Analytical data for **4**: Mp.: 105-106°C. R_F (petrol ether/ethyl acetate 1:1): 0.59. $[\alpha]_D^{27}$(c = 1.6, THF): -37.2. IR (KBr): 3334, 3291, 2954, 2940, 1749, 1685, 1654, 1546, 1523, 1471, 1365, 1274, 1151, 1049. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ = 0.93 (d, J = 6.3 Hz, 3H), 0.94 (d, J = 6.3 Hz, 3H), 1.45 (s, 9H), 1.54 (s, 3H), 1.55 (s, 3H), 1.57-1.77 (m, 3H), 4.09 (m, 1H), 4.62 (m, 2H), 5.00 (d, J = 6.0 Hz), 5.23 (dd, J = 1.3 Hz, J = 10.4 Hz, 1H), 5.32 (dd, J = 1.3 Hz, J = 17.1 Hz, 1H), 5.90 (m, 1H), 6.88 (s, 1H). ^{13}C NMR (125.8 MHz, $CDCl_3$, TMS): δ = 22.1, 22.9, 24.6, 24.8 (2C), 28.3, 41.0, 52.9, 56.3, 66.0, 80.0, 118.3, 131.9, 155.9, 171.8, 173.9. MS(CI, NH_3): *m/z* (%): 357 (63) $[M+H]^+$, 301 (100) $[M+H-C_4H_8]^+$, 257 (41) $[M+H-Boc]^+$. Anal. calcd. for $C_{18}H_{32}N_2O_5$: C, 60.65; H, 9.05; N, 7.86; found: C, 60.65; H, 8.91; N, 7.82.

Preparation of Boc-Leu-Aib-OH 5:

Boc-Leu-Aib-OH **5** was synthesized from **4** following the procedure described in Lit[2] and crystallized from TBME/MeCN.Yield: 53%.

Analytical data for **5**: Mp.: 155 °C (Lit:[3] 142-145°C). IR (KBr): 3306, 3074, 2961, 2935, 2872, 1720, 1659, 1536, 1472, 1458, 1392, 1367, 1250, 1172, 1120, 1047, 1023, 950, 922, 874, 852, 797. $[\alpha]_D^{26}$ = -32.0 (c = 1, methanol), Lit:[3] $[\alpha]_D^{23}$ = -30.4 (c = 1, methanol). ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ = 0.95 (d, J = 6.6 Hz, 3H), 0.93 (d, J = 6.3 Hz, 3H), 1.38-1.80 (m, 3H), 1.44 (s, 9H), 1.57 (s, 3H), 1.58 (s, 3H), 4.26 (m, 1H), 5.36 (d, J = 6.3 Hz, 1H), 7.25 (s, 1H), 10.02 (s, br, 1H). ^{13}C NMR (125.8 MHz, $CDCl_3$, TMS): δ = 22.1, 22.8, 24.4 (2C), 24.7, 28.3, 41.1, 52.9, 56.7, 80.5, 156.3, 172.8, 177.2. MS(CI, NH_3): *m/z* (%): 317 (38) $[M+H]^+$, 261 (93) $[M+H-C_4H_8]^+$, 217 (100) $[M+H-Boc]^+$. Anal. Calcd. for $C_{15}H_{28}N_2O_5$: C, 56.94; H, 8.92; N, 8.85; found: C, 56.91; H, 8.65; N, 8.82.

Preparation of 8:

A mixture of iodide **6** (1.280 g, 3.91 mmol, 1.0 equiv) and DBN (0.546 mL, 4.40 mmol, 1.1 equiv) in dry toluene (30 mL) was heated to reflux for 1.5 h. After cooling to RT the oily precipitate was collected by removal of the solvent and dried in vacuo to yield 1.322 g (2.93 mmol, 75%) of amidinium salt **7** which was used without further purification.

Crude **7** (111 mg, 0.25 mmol) was treated with TFA/CH_2Cl_2 (2:1 v/v, 3 mL) for 2 h. The reaction was monitored by MALDI-ToF-MS. The volatiles were removed in vacuo and the residue was lyophilized from water.

The lyophilizate was redissolved in DMF (2 mL) and Boc-Leu-Aib-OH **5** (90 mg, 0.30 mmol), N-HATU (114 mg, 0.30 mmol) and DIPEA (157 µL, 0.90 mmol) were added at 0°C. The reaction was monitored by MALDI-ToF-MS. After completion of the reaction (4 d) the volatiles were removed in vacuo and the residue was treated again with TFA/CH_2Cl_2 (2:1 v/v, 3 mL) for 30 min. After removal of the volatiles in vacuo and lyophilization from water the product **8** was isolated by RP-HPLC (method A). Yield: 44 mg (68 µmol, 27%).

Analytical data for **8**: Analytical HPLC (method A): t_R = 23.67 min. ^{1}H NMR (500 MHz, CD_2Cl_2, TMS): δ = 0.86 (d, J = 6.5 Hz, 3H), 0.88 (d, J = 6.6 Hz, 3H), 0.91 (d, J = 5.8 Hz, 3H), 0.93 (d, J = 5.9 Hz, 3H), 1.13 (ddd, J = 4.2 Hz, J = 9.4 Hz, J = 13.7 Hz, 1H), 1.40 (s, 3H), 1.45 (s, 3H), 1.61 (m, 1H), 1.66-1.77 (m, 4H), 1.98 (m, 1H), 2.04-2.18 (m, 2H), 2.23 (m, 1H), 2.82 (m, 1H), 3.13-3.23 (m, 2H), 3.26-3.35 (m, 2H), 3.43-3.51 (m, 1H), 3.63 (m, 1H), 3.73-3.91 (m, 4H), 4.20 (m, 1H), 7.52 (d, J = 8.7 Hz, 1H), 8.89 (s, br, 3H). ^{13}C NMR (125.8 MHz, CD_2Cl_2, TMS): δ = 18.4, 19.2, 21.7, 22.1, 22.3, 22.6, 23.0, 23.3, 24.7, 25.2, 25.4 (2C), 31.3, 40.1, 40.7, 42.8, 44.5, 44.8, 45.5, 53.9, 55.0, 56.5, 57.7, 165.7, 169.3, 175.2. MS (ESI): *m/z* : found 422.3, monoisotopic mass calculated for the cation $C_{23}H_{44}N_5O_2^+$: 422.35.

Preparation of 9:

Solid phase synthesis of Z-Aib-Aib-Pip-Aib-Gly-OH **9** was carried out on glycine-loaded *o*-chloro trityl resin. Starting with 500 mg (0.6 mmol/g resin, 0.3 mmol, 1 equiv) of resin, 19 mg (33 µmol, 11 %) of purified **9** were obtained.

Analytical data for **9:** Analytical HPLC (method A): t_R = 32.56 min. ^{1}H NMR (500 MHz, CD_2Cl_2, TMS): δ = 1.37-1.65 (m, 24H), 2.15-2.23 (m, 1H), 3.10 (m, 1H), 3.87 (dd, J = 5.6 Hz, J = 17.5 Hz, 1H), 3.98 (m, 1H), 4.05 (dd, J = 6.2 Hz, J = 17.5 Hz, 1H), 4.89 (m, 1H), 5.06 (d, J = 12.1 Hz, 1H), 5.11 (d, J = 12.1 Hz, 1H), 6.84 (s, 1H), 7.26 (t, J = 5.3 Hz, 1H), 7.31-7.40 (m, 6H), 7.79 (s, 1H). ^{13}C NMR (125.8 MHz, CD_2Cl_2, TMS): δ = 20.6, 24.8, 25.3, 25.6, 25.8, 26.3, 27.4, 42.6, 44.5, 56.1, 57.3, 57.5, 57.6, 67.4, 128.4, 128.7, 129.0, 136.8, 155.6, 171.8, 172.7, 173.7, 175.3, 176.3. MS (MALDI-ToF): *m/z*: found 598.4 $[M+Na]^+$, 620.4 $[M-H+2Na]^+$, monoisotopic mass calculated for $C_{28}H_{41}N_5O_8$: 575.30.

Preparation of 10:

Solid phase synthesis of Ac-Pip-Aib-Pip-Aib-Aib-Leu-β-Ala-Gly-OH **10** was carried out on glycine-loaded *o*-chloro trityl resin. Starting with 300 mg (0.6 mmol/g resin, 180 µmol, 1 equiv) of resin, 19 mg (23 µmol, 13 %) of purified **10** were obtained.

Analytical data for **10**: Analytical HPLC (method C): t_R = 23.01 min. ^{1}H NMR (500 MHz, CD_2Cl_2, TMS): δ = 0.85 (d, J = 5.7 Hz, 3H), 0.93 (d, J = 5.9 Hz, 3H), 1.38-1.82 (m, 15H), 1.43 (s, 3H), 1.45 (s, 3H), 1.46 (s, 3H), 1.47 (s, 3H), 1.48 (s, 3H), 1.51 (s, 3H), 2.07-2.16 (m, 2H), 2.18 (s, 3H), 2.49 (m, 1H), 2.58 (m, 1H), 3.05 (m, 1H), 3.20 (ddd, J = 3.2 Hz, J = 10.3 Hz, J = 13.5 Hz, 1H), 3.29 (m, 1H), 3.71 (m, 1H), 3.79 (m, 1H), 3.93-4.10 (m, 3H), 4.19 (m, 1H), 4.66 (m, 1H), 5.20 (m, 1H), 7.42 (t, J = 4.6 Hz, 1H), 7.57 (d, J = 7.6 Hz, 1H), 7.72 (t, J = 5.0 Hz, 1H), 7.95 (s, 1H). ^{13}C NMR (125.8 MHz, CD_2Cl_2, TMS): δ = 176.6, 176.0, 175.1, 173.9, 173.2 (2C), 172.5, 172.0, 171.8, 57.8, 57.6, 57.3 (2C), 52.1, 45.1, 43.0, 42.7, 40.0, 36.8 (2C), 27.9, 27.8, 26.8, 25.5 (2C), 25.45 (2C), 25.4, 24.4, 23.5, 23.4, 23.0, 21.9, 20.8 (2C), 20.5, 19.7. MS (MALDI-ToF): *m/z*: found 779.5 $[M+H]^+$, 801.6 $[M+Na]^+$, 823.6 $[M+K]^+$, monoisotopic mass calculated for $C_{37}H_{62}N_8O_{10}$: 778.46.

Preparation of 11:

DIPEA (35 µL, 203 µmol, 4.2 equiv) was added at 0°C to a stirred solution of Z-Aib-Aib-Pip-Aib-Gly-OH **9** (30 mg, 52 µmol, 1.1 equiv) and N-HATU (22 mg, 58 µmol, 1.2 equiv) in DMF (0.5 mL). After 5 min the amidinium salt **8** (31 mg, 48 µmol, 1.0 equiv),

dissolved in dry dichloromethane (1.5 mL), was added. The reaction was monitored by MALDI-ToF-MS. After completion of the reaction (1 h) the volatiles were removed in vacuo. The residue was redissolved in methanol (2 mL) containing 0.3 mL of acetic acid, treated with palladium (10% on charcoal, 30 mg) under hydrogen atmosphere. After stirring overnight the catalyst was filtered off and washed with methanol. The solvent was removed by rotary evaporation and the product was isolated by RP-HPLC (method A). Yield: 22 mg (21 µmol, 44%).

Analytical data for **11**: Analytical HPLC (Method B): t_R = 21.95 min. ^{1}H NMR (500 MHz, CD_2Cl_2, TMS): δ = 0.86 (d, J = 6.5 Hz, 3H), 0.88 (d, J = 6.6 Hz, 3H), 0.91 (d, J = 6.6 Hz, 3H), 0.93 (d, J = 6.6 Hz, 3H), 1.18 (ddd, J = 3.4 Hz, J = 10.1 Hz, J = 13.5 Hz, 1H), 1.31-1.82 (m, 8H), 1.45 (s, 6H), 1.46 (s, 3H), 1.48 (s, 3H), 1.50 (s, 3H), 1.51 (s, 3H), 1.65 (s, 6H), 1.88 (ddd, J = 4.2 Hz, J = 9.9 Hz, J = 14.6 Hz, 1H), 2.04 (m, 1H), 2.08-2.23 (m, 3H), 2.32 (m, 1H), 2.81 (m, 1H), 3.20-3.47 (m, 7H), 3.55-3.83 (m, 5H), 3.86-3.95 (m, 2H), 4.09 (m, 1H), 4.34 (m, 1H), 4.57 (m, 1H), 6.76 (d, J = 9.3 Hz, 1H), 7.12 (s, 1H), 7.70 (s, 1H), 7.96 (t, J = 4.7 Hz, 1H), 8.11 (d, J = 4.8 Hz, 1H), 8.91 (s, 1H), 9.28 (s, br, 3H). ^{13}C NMR (125.8 MHz, CD_2Cl_2, TMS): δ = 177.3, 175.7, 174.5, 173.5, 173.2 (2C), 171.8, 166.1, 57.8, 57.7, 57.5, 57.3, 57.2, 45.0, 44.5, 44.4, 42.8, 41.6, 39.9, 31.3, 28.2, 26.8, 26.5, 25.3, 25.1, 25.0, 24.6, 24.5, 24.3, 23.5 (2C), 23.3, 21.5, 21.3, 19.3, 18.4. MS (ESI): *m/z* : found 845.8, monoisotopic mass calculated for the cation $C_{43}H_{77}N_{10}O_7^+$: 845.60.

Determination of F_1-ATPase activity

F_1-ATPase complexes from *Escherichia coli* were prepared according to Lit[4]. ATPase activities were determined by use of an automated assay[5,6] detecting the formation of a phosphomolybdenum blue complex photometrically at 578 nm. Linear enzyme turnover, i. e. increase of inorganic phosphate released by enzyme activity, was monitored over a period of 7 min at 37 °C. For calibration of the system, a 50 µM KH_2PO_4 solution was used as a standard. For efrapeptin C inhibition, purified F_1-ATPase (1.2 µM in 1 ml 50 mM Tris/HCl pH 8.0) was incubated in the presence of increasing amounts of **1** for 20 min at 37 °C. Subsequently, 9 ml 50 mM Tris/HCl pH 8.0, 100 mM $MgCl_2$, 100 mM ATP were added and the samples were assayed as described.

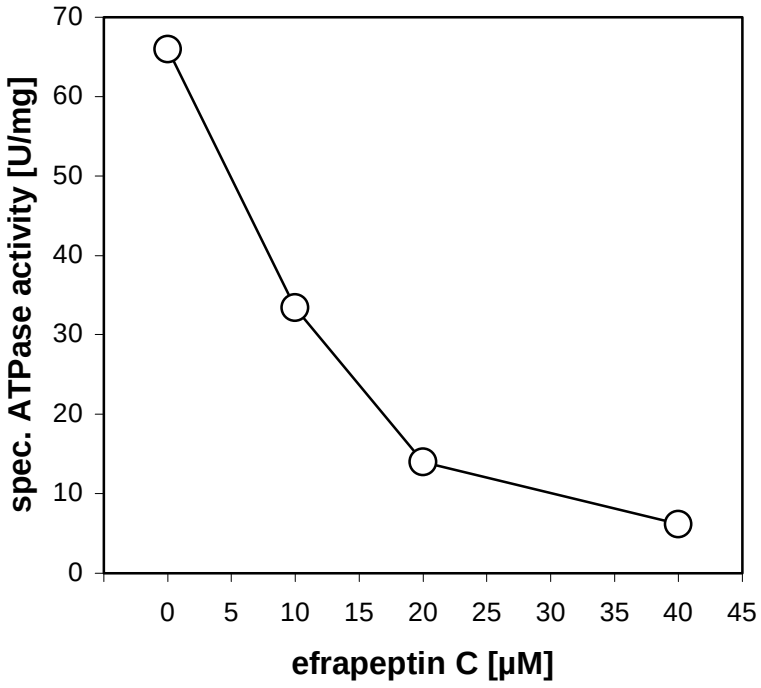

Figure S1: Inhibition of *E. coli* F_1-ATPase by synthetic efrapeptin C **1**.

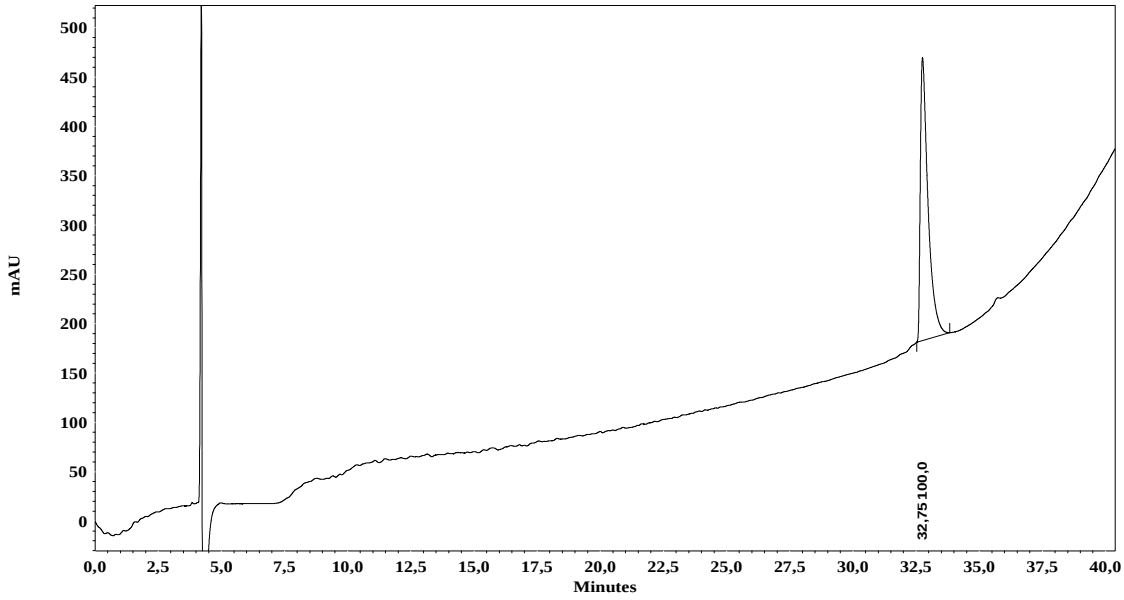

Figure S2: HPLC-trace of synthetic efrapeptin C **1**.

Spectra

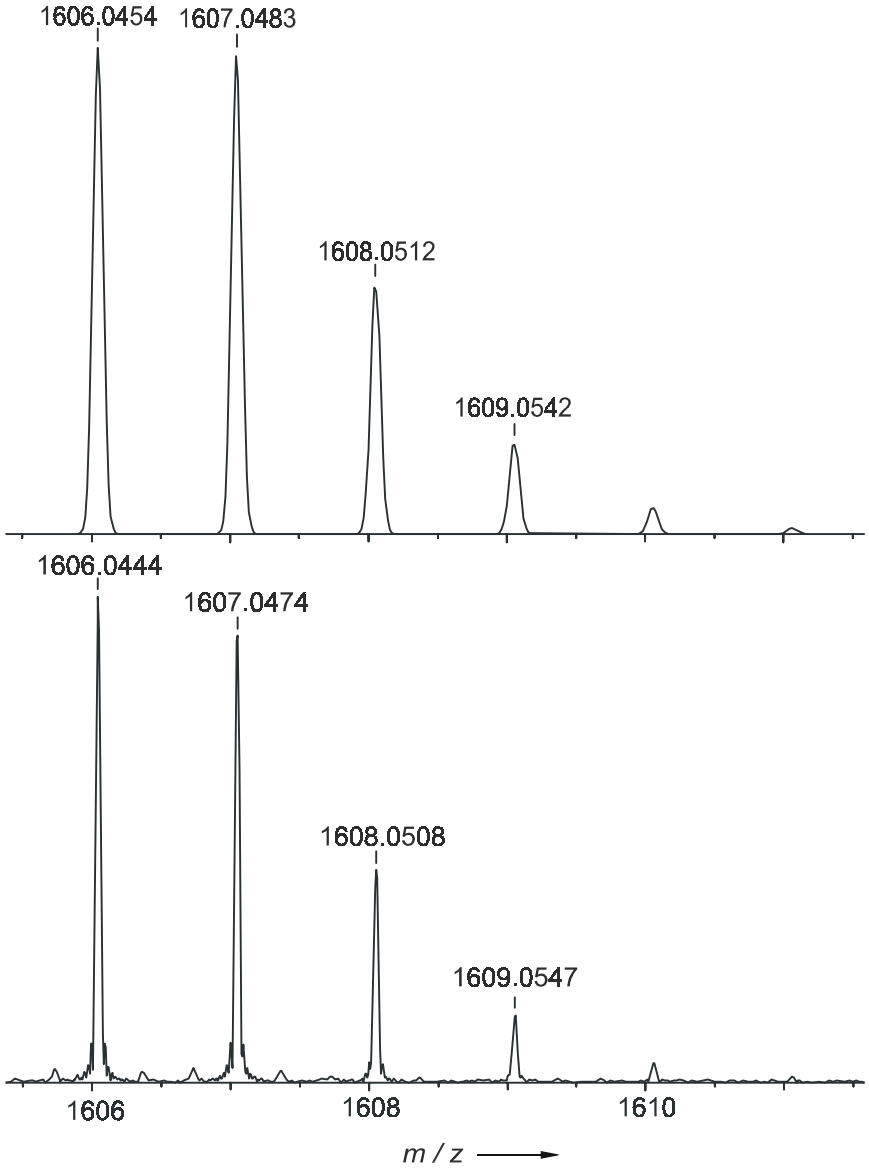

Figure S3: Simulated (upper trace) and experimental (lower trace) ESI-FT-ICR mass spectrum of efrapeptin C **1**.

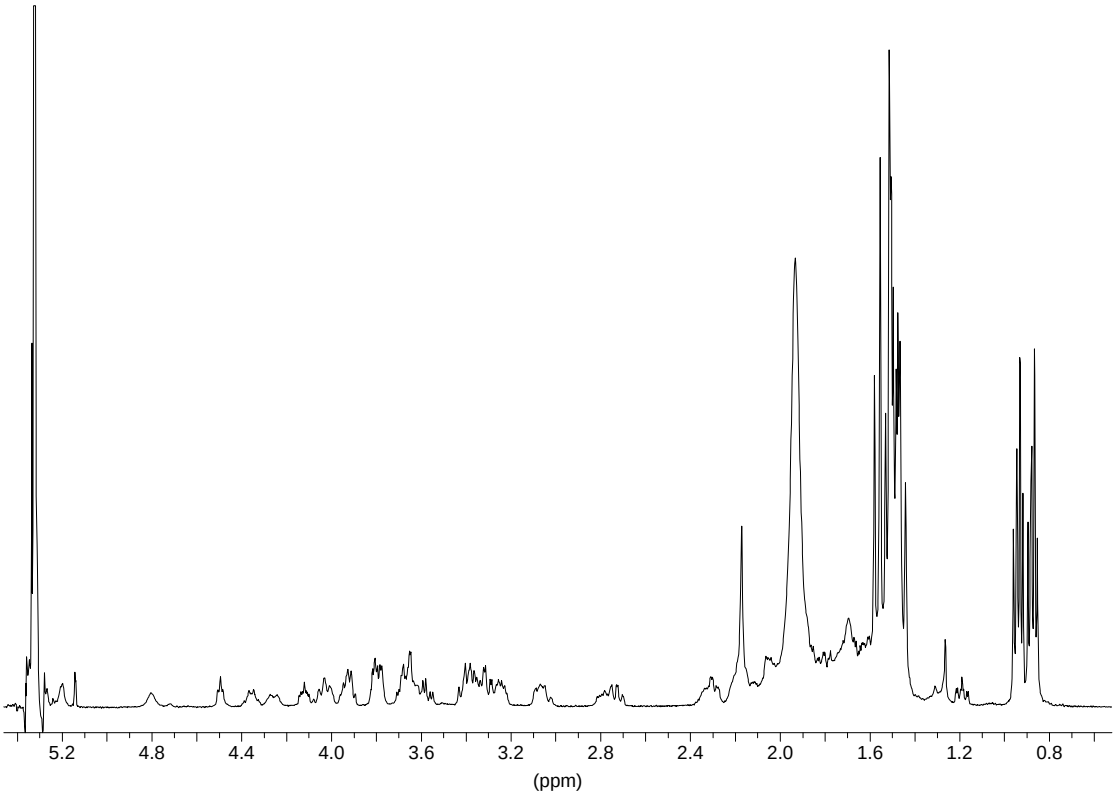

Figure S4: ^{1}H NMR spectrum (500 MHz) of synthetic **1** in CD_2Cl_2 (0.5-5.5 ppm).

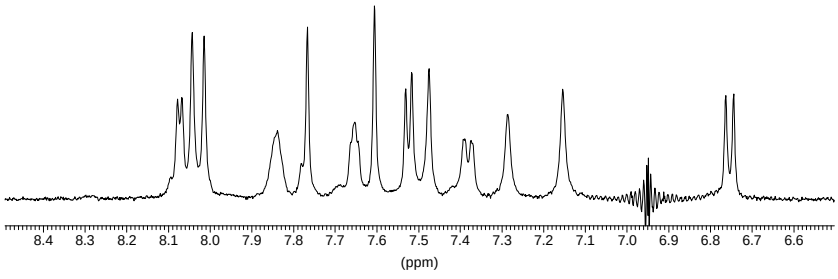

Figure S5: ^{1}H NMR spectrum (500 MHz) of synthetic **1** in CD_2Cl_2 (6.5-8.5 ppm).

References

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