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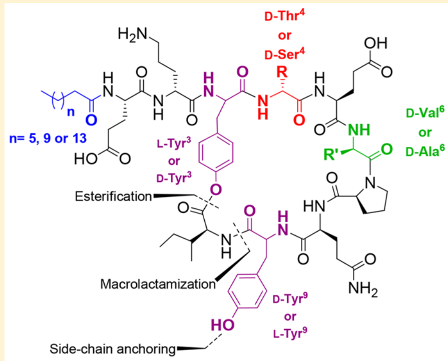
Total Solid-Phase Synthesis of Dehydroxy Fengycin Derivatives

Cristina Rosés, Cristina Camó, Àngel Oliveras, Lluis Moll, Nerea López, Lidia Feliu,* and Marta Planas*

LIPPSO, Department of Chemistry, University of Girona, Maria Aurèlia Capmany 69, 17003 Girona, Spain

Supporting Information

ABSTRACT: A rapid and efficient solid-phase strategy for the synthesis of dehydroxy fengycins derivatives is described. This synthetic approach involved the linkage of a Tyr to a Wang resin via a Mitsunobu reaction and the elongation of the peptide sequence followed by subsequent acylation of the N-terminus of the resulting linear peptidyl resin, esterification of the phenol group of a Tyr with an Ile, and final macrolactamization. The amino acid composition as well as the presence of the N-terminal acyl group significantly influenced the stability of the macrolactone. Cyclic lipodepsipeptides with a L-Tyr^3/D-Tyr^9 configuration were more stable than those containing the Tyr residues with an opposite configuration. This work constitutes the first approach on the total solid-phase synthesis of dehydroxy fengycin derivatives.



■ INTRODUCTION

Cyclic lipodepsipeptides are a structurally diverse group of nonribosomal metabolites typically produced by bacterial and fungal species, such as *Pseudomonas* or *Bacillus* strains.[1−4] This class of compounds has raised interest due to their wide range of biological activities and their structural complexity. The main structural feature of these cyclic peptides is the occurrence of an ester bond between the side chain of an amino acid and the C-terminal end of the sequence. The fatty acid moiety is commonly attached to the N-terminus of this macrolactone. Moreover, the complexity of the structure of these lipodepsipeptides is increased by the combination of L- and D-amino acids as well as of other unnatural residues present in their sequence.[5,6]

Fengycins are a family of natural cyclic lipodepsipeptides isolated from *Bacillus* strains.[5,6] They consist of an eight-residue macrocycle with a phenyl ester linkage between the phenol group of a tyrosine (Tyr) and the α-carboxylic group of an isoleucine (Ile) (Figure 1). This cyclic depsipeptide bears at its N-terminus a dipeptidyl tail acylated with a β-hydroxy fatty acid. Different fengycin isoforms have been described, fengycins A and B being the most common.[7−14] These two isoforms differ on the amino acid at position 6, which is a D-alanine (D-Ala) in fengycin A and a D-valine (D-Val) in the B isoform (Figure 1). Sang-Cheol et al. isolated from *Bacillus amyloliquefaciens* fengycin S.[15] Compared to fengycin B, this isoform bears a D-serine (D-Ser) at position 4 instead of a D-*allo*-threonine (D-*allo*-Thr). The configuration of Tyr residues at positions 3 and 9 of fengycins has been a controversial issue. Fengycins were first reported to incorporate a D-Tyr^3 and an L-Tyr^9, whereas the opposite configuration (L-Tyr^3/D-Tyr^9) was assigned to another family of related peptides named as plipastatins.[7,16] However, it has been recently confirmed that

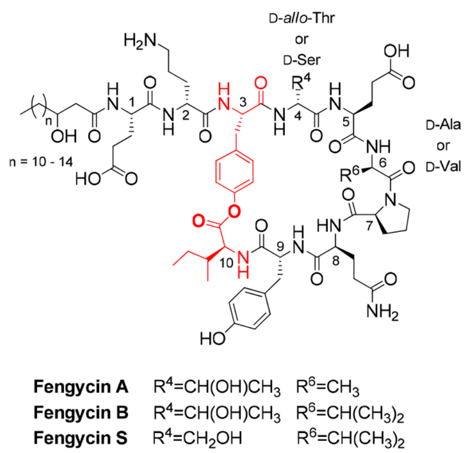


Figure 1. Structure of fengycins A, B, and S.

the configuration of Tyr^3 and Tyr^9 in fengycins and plipastatins is identical, being L-Tyr^3/D-Tyr^9.[17−20] Since the term fengycins is more widely used than plipastatins, herein we employed the former term for the peptides of this study but using the correct configuration.

Fengycin lipopeptides have attracted considerable interest due to their strong antifungal activity and their low hemolysis compared to other lipopeptides isolated from *Bacillus* spp.[7,21,22] Their significant antifungal activity has been ascribed to their propensity to form stable membrane-bound aggregates.[23] Moreover, they have been described as elicitors of plant defense responses.[24,25] The use of compounds with

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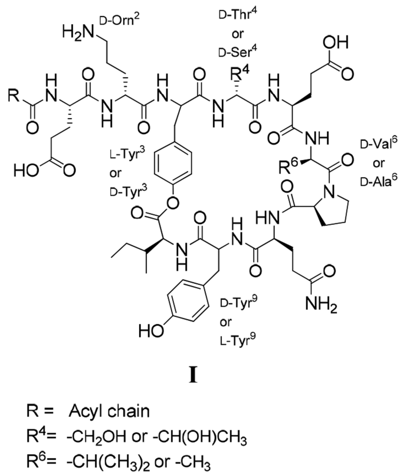
such activity is considered as a promising alternative approach for the protection of crops against phytopathogens.[2,26,27]

Despite their interest, to date and to the best of our knowledge, the synthesis of fengycins has only been accomplished by the group of Marahiel and Essen. Their strategy comprised the solid-phase preparation of the linear precursor and its enzymatic cyclization in solution.[5,28,29] The lack of suitable synthetic protocols for fengycins could be attributed to the presence of a highly labile phenyl ester function in their structure. In fact, the synthesis of cyclic depsipeptides, either in solution or on solid phase, has only been reported for those peptides bearing an ester bond involving the ß-hydroxyl group of a Ser or a Thr residue.[30−34] Recently, we established a convenient solid-phase strategy for the preparation of the macrolactone of eight amino acids present in fengycins.[35] The key steps of the synthesis were the formation of the phenyl ester bond and the on-resin head-to-side-chain cyclization.

In view of these previous results, we decided to study the application of this methodology to the total solid-phase synthesis of dehydroxy fengycin derivatives with the general structure **I** (Figure 2). These derivatives are fengycin A, B, and S analogues that contain a D-Thr[4] instead of a D-*allo*-Thr[4] and a dehydroxy fatty acid chain. Synthesis of analogues containing both an L-Tyr[3]/D-Tyr[9] or a D-Tyr[3]/L-Tyr[9] configuration was studied. This approach would benefit from the advantages inherent to the solid-phase methodology and would allow rapid access to a variety of fengycin analogues.



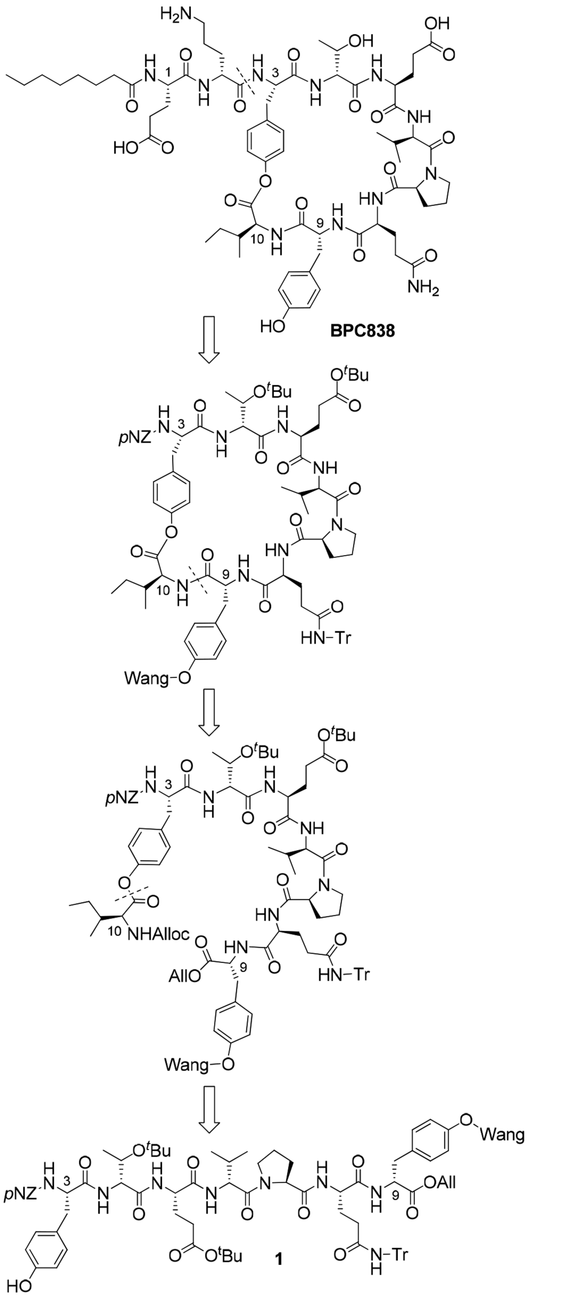
I

Figure 2. General structure of dehydroxy fengycin derivatives **I**.

RESULTS AND DISCUSSION

Synthesis of Cyclic Lipodepsipeptides Bearing a L-Tyr[3]/D-Tyr[9]. Our investigations started with the solid-phase synthesis of the cyclic lipodepsipeptide **BPC838** containing D-Thr[4], D-Val[6], D-Tyr[9], and an octanoyl group (Scheme 1). This synthesis was chosen as a model to check the feasibility of our approach. On the basis of our previous experience on the preparation of cyclic depsipeptides, the retrosynthetic route that we envisaged involved the following as the main steps: (i) preparation of the heptapeptidyl resin **1** with the N-terminal L-Tyr[3] protected with a *p*-nitrobenzyloxycarbonyl (*p*NZ) group, (ii) ester bond formation between L-Tyr[3] and Ile[10], (iv) simultaneous deprotection of Ile[10] and D-Tyr[9] followed by the on-resin cyclization, and (vi) elongation of the peptide

Scheme 1. Retrosynthetic Analysis of BPC838



sequence and its final acylation. As protecting groups, allyl (All) and allyloxycarbonyl (Alloc) were selected for Tyr[9] and Ile[10], respectively, because they can be simultaneously removed in the presence of palladium and are orthogonal with the 9-fluorenylmethoxycarbonyl (Fmoc) and *tert*-butyl (^{t}Bu) groups. The *p*NZ group was chosen to protect Tyr[3] because it has been reported to be orthogonal to Fmoc as well as to ^{t}Bu and allyl-based protecting groups, and its removal can be achieved under neutral conditions using $SnCl_2$ in the presence of catalytic amounts of acid.[36]

According to this route, Fmoc-D-Tyr-OAll was anchored to a Wang resin by treatment with PPh_3 and diisopropylazodicarboxylate (DIAD) in anhydrous tetrahydrofuran (THF) under microwave irradiation for 30 min at 60 °C (Scheme 2).[35] The loading of the resulting resin Fmoc-D-Tyr(Wang)-OAll was 0.33 mmol/g as determined by the Fmoc method.[37] In

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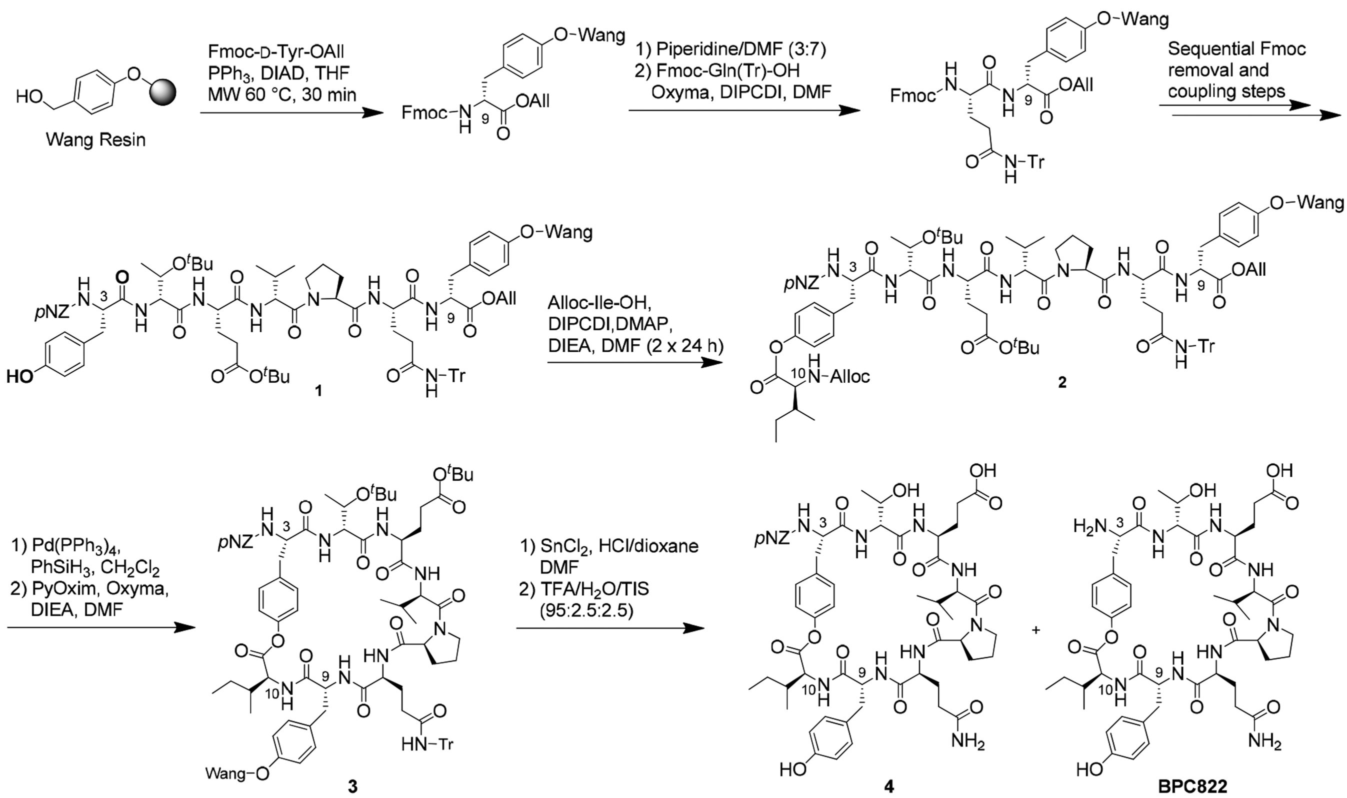
Scheme 2. Synthesis of the Cyclic Peptidyl Resin 3 and Attempts of *p*NZ Removal



addition, a Marfey's test confirmed that the D-Tyr residue did not racemize under these conditions.[38] Then the peptidyl resin *p*NZ-Tyr[3]-D-Thr(^{t}Bu)-Glu(O^{t}Bu)-D-Val-Pro-Gln(Tr)-D-Tyr[9](Wang)-OAll (**1**) was prepared following a Fmoc/^{t}Bu/allyl (All) strategy. Fmoc group removal was performed using piperidine/DMF (3:7), and the coupling of the corresponding amino acids was mediated by *N,N*′-diisopropylcarbodiimide (DIPCDI) and 2-cyano-2-(hydroxyimino)acetate (Oxyma) in DMF. All amino acids, except for Tyr[3], were incorporated as Fmoc derivatives with the side-chain group protected with trityl (Tr) for Gln and ^{t}Bu for Glu and Thr. Tyr[3] was introduced as *p*NZ-Tyr-OH to allow the required esterification of the phenol group. This tyrosine derivative was prepared from commercially available H-Tyr(O^{t}Bu)-OH by treatment with *p*NZ-N_3,[36] followed by side-chain deprotection under acidic conditions (68% overall yield). After completion of the peptide sequence, acidolytic cleavage with trifluoroacetic acid (TFA)/H_2O/triisopropylsilane (TIS) (95:2.5:2.5) of an aliquot of resin **1** afforded the expected peptide *p*NZ-Tyr-D-Thr-Glu-D-Val-Pro-Gln-D-Tyr-OAll in 65% HPLC purity.

Then Alloc-Ile-OH was incorporated to **1** using the conditions previously described for the preparation of cyclic depsipeptides analogous to the cyclic moiety of fengycins (Scheme 2).[35] Therefore, esterification of **1** with Alloc-Ile-OH was achieved employing DIPCDI, 4-dimethylaminopiridine (DMAP), and *N,N*-diisopropylethylamine (DIEA) in DMF. Two treatments of 24 h were necessary to obtain a complete conversion. An aliquot of the resulting resin *p*NZ-Tyr[3](O-Ile[10]-Alloc)-D-Thr(^{t}Bu)-Glu(O^{t}Bu)-D-Val-Pro-Gln(Tr)-D-Tyr[9](Wang)-OAll (**2**) was treated under acidolytic conditions yielding the expected linear depsipeptide *p*NZ-Tyr(O-Ile-Alloc)-D-Thr-Glu-D-Val-Pro-Gln-D-Tyr-OAll in 87% HPLC purity.

Next, the Alloc and allyl protecting groups of resin **2** were simultaneously removed using a catalytic amount of $Pd(PPh_3)_4$ in the presence of $PhSiH_3$ in CH_2Cl_2 for 4 h (Scheme 2). After acidolytic cleavage of an aliquot of the resulting resin *p*NZ-Tyr[3](O-Ile[10]-H)-D-Thr(^{t}Bu)-Glu(O^{t}Bu)-D-Val-Pro-Gln(Tr)-D-Tyr[9](Wang)-OH, the corresponding peptide was obtained in 72% HPLC purity. Subsequent on-resin cyclization was assayed using [ethyl cyano(hydroxyimino)acetato-O^2]tri-(1-pyrrolidinyl)-phosphonium hexafluorophosphate (PyOxim), Oxyma, and DIEA, yielding the cyclic peptidyl resin **3**. Treatment of an aliquot of this resin with TFA/H_2O/TIS afforded the cyclic depsipeptide *p*NZ-Tyr[3](&)-D-Thr-Glu-D-Val-Pro-Gln-D-Tyr[9]-Ile[10]-& (**4**) in 31% HPLC purity, as shown by ESI-MS where a peak at *m/z* 1195.5 corresponding to $[M + Na]^+$ was observed (& symbol indicates the location of the ester linkage[39]). The linear peptide precursor was not detected either by HPLC or by mass spectrometry. To confirm the structure of **4**, the crude reaction mixture resulting from acidolytic cleavage was treated with $CH_3OH/H_2O/NH_3$ (4:1:1), conditions that are known to hydrolyze ester bonds.[40−42] HPLC and mass spectrometry analysis of the resulting crude revealed only the presence of the linear peptide resulting from the hydrolysis of the ester bond in **4**, *p*NZ-Tyr[3]-D-Thr-Glu-D-Val-Pro-Gln-D-Tyr[9]-Ile[10]-OH, and of the corresponding methyl ester *p*NZ-Tyr[3]-D-Thr-Glu-D-Val-Pro-Gln-D-Tyr[9]-Ile[10]-OMe. Therefore, this result demonstrated the formation of the cyclic depsipeptide **4**.

We then attempted the *p*NZ group removal of resin **3** using $SnCl_2$ (6 M) in HCl/dioxane (1.6 mM) and DMF for 1 h at room temperature. Unexpectedly, this deprotection was troublesome, and even after repeating this treatment 5 more times, the deprotected cyclic peptide **BPC822** was obtained

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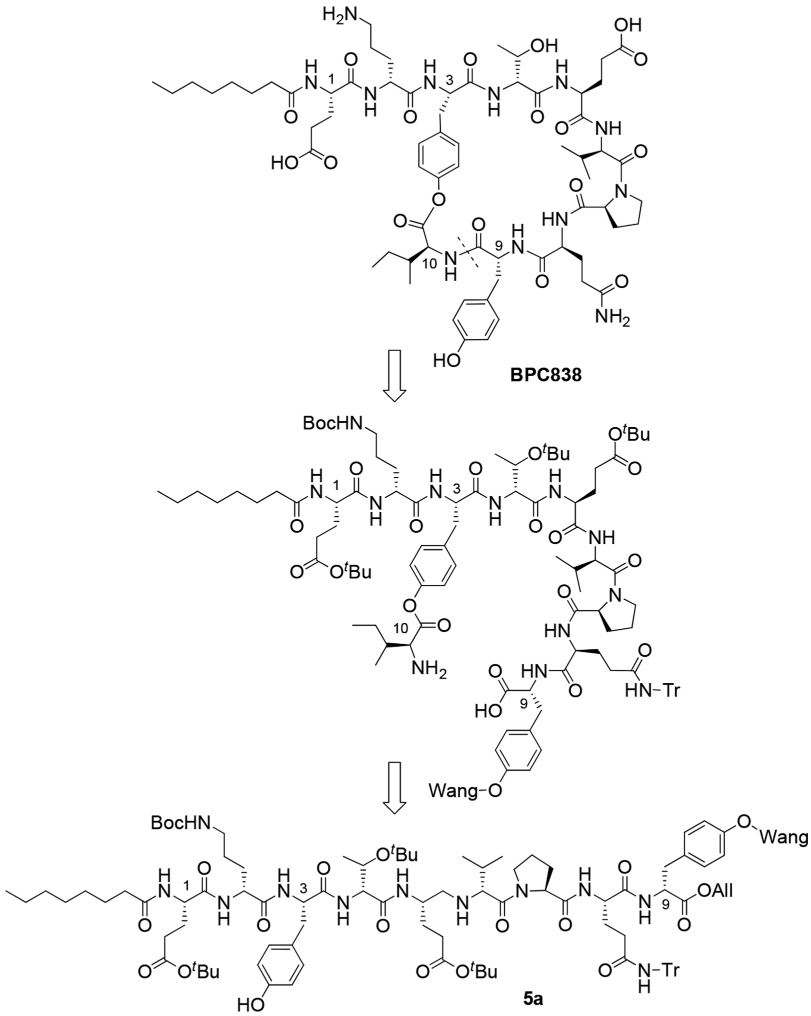
Scheme 3. Alternative Retrosynthetic Analysis of BPC838



together with an important amount of the *p*NZ-protected cyclic depsipeptide **4** as shown by mass spectrometry.

On the basis of these results, we envisaged an alternative route to obtain the cyclic lipodepsipeptide **BPC838** (Scheme 3). In this approach, instead of building the macrolactone and then incorporating the tail, we planned the synthesis of the linear peptidyl resin **5a** already bearing the acylated dipeptidyl tail. Then this resin would be esterified at Tyr^{3} with Ile^{10} and finally cyclized to render the desired cyclic lipodepsipeptide.

For this purpose, as depicted in Scheme 4, we first synthesized the linear peptidyl resin Fmoc-Glu^{1}(O^{t}Bu)-D-Orn(Boc)-Tyr^{3}-D-Thr(^{t}Bu)-Glu(O^{t}Bu)-D-Val-Pro-Gln(Tr)-D-Tyr^{9}(Wang)-OAll (**6**) through side-chain anchoring of Fmoc-D-Tyr-OAll to a Wang resin followed by sequential Fmoc removal and coupling steps using the conditions mentioned above for resin **1**. Orn and Tyr^{3} were incorporated as Fmoc-Orn(Boc)-OH and Fmoc-Tyr-OH, respectively. An aliquot of the resulting linear peptidyl resin **6** was treated with TFA/H_2O/TIS (95:2.5:2.5) for 2 h, affording the linear peptide Fmoc-Glu-D-Orn-Tyr-D-Thr-Glu-D-Val-Pro-Gln-D-Tyr-OAll in 74% HPLC purity.

With peptidyl resin **6** in hand, we proceeded to its acylation with octanoic acid (Scheme 4). Thus, after Fmoc group removal octanoic acid was incorporated using Oxyma/DIPCDI in DMF under stirring at room temperature overnight. Acidolytic treatment of an aliquot of the resulting resin **5a** afforded the linear lipopeptide C_7H_{15}CO-Glu-D-Orn-Tyr-D-Thr-Glu-D-Val-Pro-Gln-D-Tyr-OAll in 79% HPLC purity. Next, the esterification of **5a** with Alloc-Ile-OH was performed employing DIEA, DIPCDI, and DMAP (2 × 24 h). An aliquot of the resulting resin C_7H_{15}CO-Glu^{1}(O^{t}Bu)-D-Orn(Boc)-Tyr^{3}(O-Ile^{10}-Alloc)-D-Thr(^{t}Bu)-Glu(O^{t}Bu)-D-Val-Pro-Gln-(Tr)-D-Tyr^{9}(Wang)-OAll (**7a**) was acidolytically cleaved, yielding the branched lipodepsipeptide C_7H_{15}CO-Glu-D-Orn-Tyr(O-Ile-Alloc)-D-Thr-Glu-D-Val-Pro-Gln-D-Tyr-OAll in 81% HPLC purity.

Selective removal of both Alloc and allyl protecting groups in **7a** with Pd(PPh_3)$_3$ and $PhSiH_3$ in CH_2Cl_2 for 4 h followed by exposure of an aliquot of the resulting resin **8a** to TFA/H_2O/TIS afforded the expected linear peptide in 76% HPLC purity (Scheme 4). Resin **8a** was then treated with Oxyma, PyOxim, and DIEA in DMF for 24 h to prompt its cyclization. Acidolytic cleavage of the resulting resin afforded the desired cyclic lipodepsipeptide C_7H_{15}CO-Glu-D-Orn-Tyr(&)-D-Thr-Glu-D-Val-Pro-Gln-D-Tyr-Ile-& (**BPC838**) in 33% HPLC purity. Analysis by mass spectrometry of the crude reaction mixture showed the formation of **BPC838** as a major product. Interestingly, only traces of the linear peptide resulting from hydrolysis of the macrolactone were observed. Purification by reverse-phase column chromatography (RP-HPLC) yielded **BPC838** in >99% HPLC purity. The structure of this peptide was verified by 1D and 2D NMR experiments. This result

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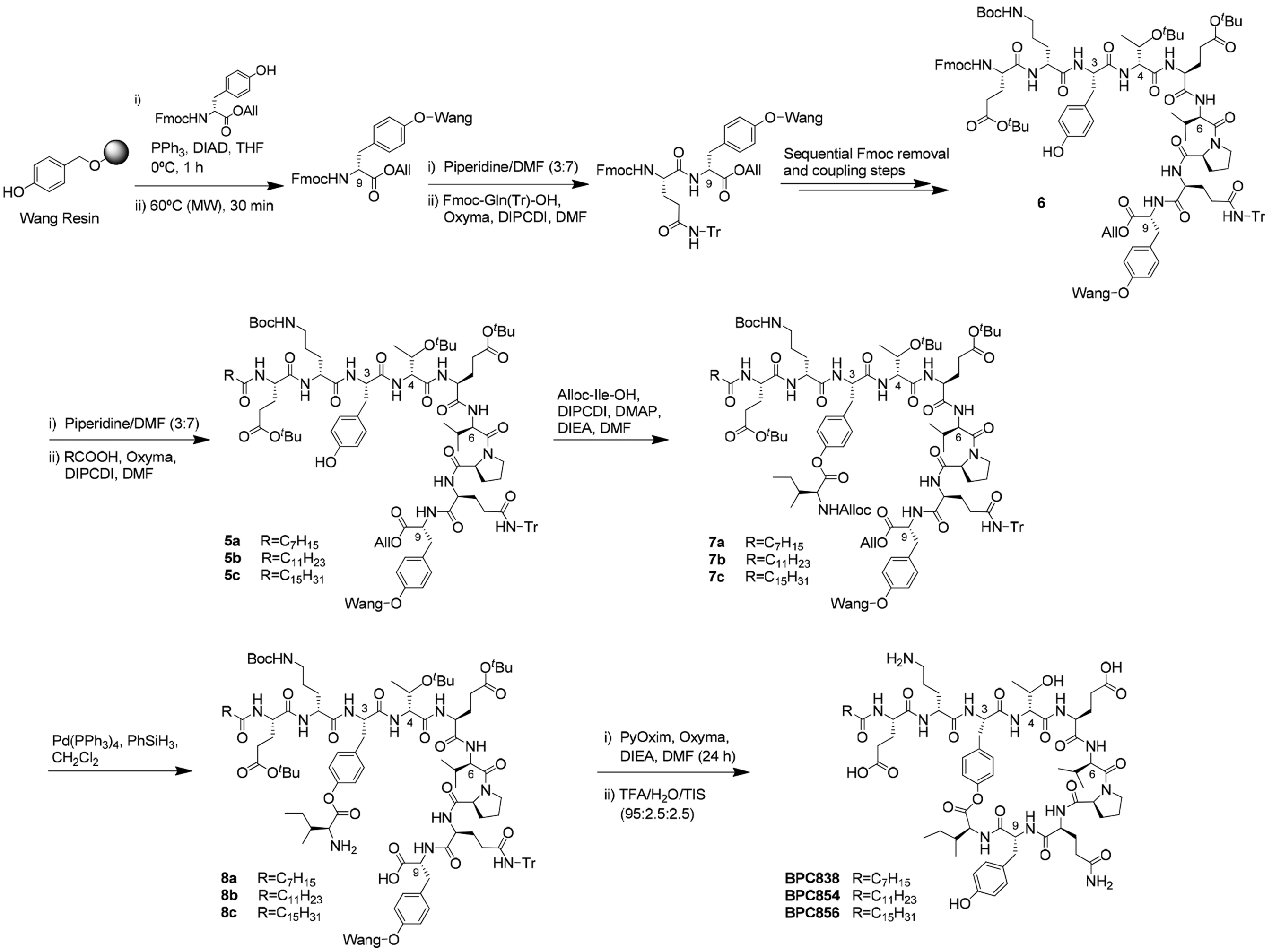
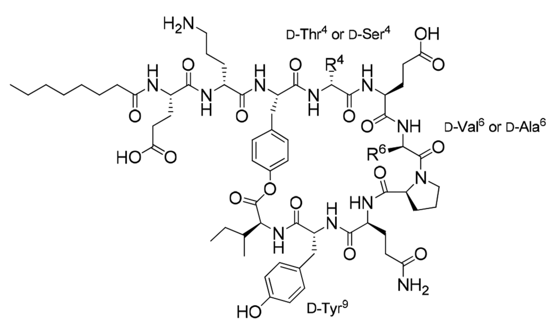
Scheme 4. Structure and General Synthetic Approach of Cyclic Lipodepsipeptides BPC838, BPC854, and BPC856



demonstrated the suitability of this strategy for the total solid-phase synthesis of dehydroxy fengycin derivatives.

This methodology was then extended to the preparation of cyclic lipodepsipeptides **BPC854** and **BPC856** bearing a lauric and palmitic acid, respectively (Scheme 4). For this purpose, after Fmoc removal of resin **6** acylation of the resulting free amino group was performed using lauric and palmitic acid in the presence of DIPCDI and Oxyma. The corresponding lipopeptidyl resins **5b** and **5c** were acydolitically cleaved, yielding the expected lipopeptides in 90% and 93% HPLC purity, respectively. Subsequent esterification of **5b** and **5c** with Alloc-Ile-OH followed by allyl and Alloc group removal and on-resin cyclization provided, after cleavage with TFA/H_2O/TIS (95:2.5:2.5), the cyclic lipodepsipeptides $C_{11}H_{23}$CO-Glu-D-Orn-Tyr(&)-D-Thr-Glu-D-Val-Pro-Gln-D-Tyr-Ile-& (**BPC854**) and $C_{15}H_{31}$CO-Glu-D-Orn-Tyr(&)-D-Thr-Glu-D-Val-Pro-Gln-D-Tyr-Ile-& (**BPC856**) in 49% and 50% HPLC purity, respectively. Both crude peptides were purified by RP-HPLC and characterized by mass spectrometry, yielding **BPC854** and **BPC856** in good purities (92% HPLC purity). To confirm the presence of the ester bond, these cyclic lipodepsipeptides were subjected to basic hydrolysis using $CH_3OH/H_2O/NH_3$ (4:1:1). HPLC and mass spectrometry analysis of the resulting crudes revealed only the presence of the linear peptide resulting from the hydrolysis of the ester bond, demonstrating the formation of the cyclic lipodepsipeptide. These peptides were fully characterized by NMR spectroscopy.

Similarly, we prepared analogues of **BPC838** differing on the amino acids at positions 4 and 6 (Figure 3). In particular, **BPC840** (D-Ser^4, D-Val^6, D-Tyr^9), **BPC842** (D-Thr^4, D-Ala^6, D-Tyr^9), and **BPC844** (D-Ser^4, D-Ala^6, D-Tyr^9) were synthesized following the above methodology and obtained in 35%, 26%, and 21% HPLC purity, respectively. ESI-MS analysis showed



BPC840 R^4= CH_2OH R^6= $CH(CH_3)_2$
BPC842 R^4= $CH(OH)CH_3$ R^6= CH_3
BPC844 R^4= CH_2OH R^6= CH_3

Figure 3. Structure of cyclic lipodepsipeptides **BPC840**, **BPC842**, and **BPC844**.

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the presence of the corresponding cyclic lipodepsipeptide as the major product. RP-HPLC purification afforded these peptides in purities > 94%. Their structure was characterized by NMR.

Synthesis of Cyclic Lipodepsipeptides Bearing D-Tyr³/L-Tyr⁹. Taking into account the different configuration reported for Tyr³ and Tyr⁹ for natural fengycins, we decided to prepare cyclic lipodepsipeptides incorporating a D-Tyr³ and an L-Tyr⁹ (Figure 4). In particular, we attempted the synthesis of **BPC846** (D-Tyr³, D-Thr⁴, D-Val⁶, octanoyl), **BPC848** (D-Tyr³, D-Ser⁴, D-Val⁶, octanoyl), **BPC850** (D-Tyr³, D-Thr⁴, D-Ala⁶, octanoyl), **BPC852** (D-Tyr³, D-Ser⁴, D-Ala⁶, octanoyl), **BPC858** (D-Tyr³, D-Thr⁴, D-Val⁶, lauroyl), and **BPC860** (D-Tyr³, D-Thr⁴, D-Val⁶, palmitoyl).

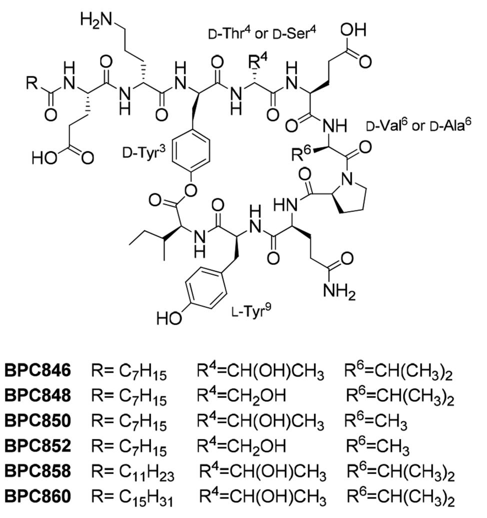
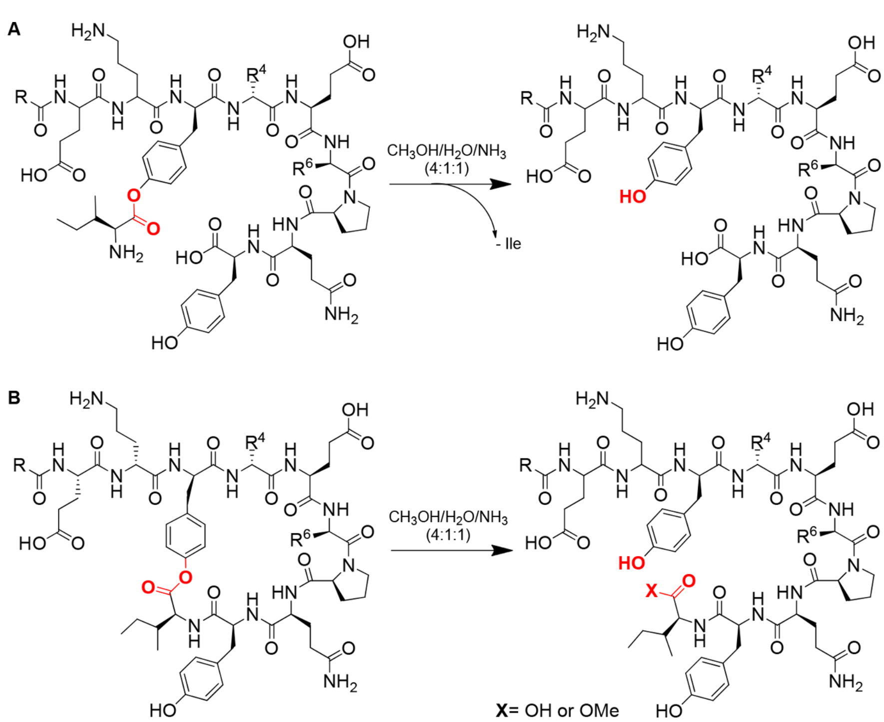


Figure 4. Structure of cyclic lipodepsipeptides **BPC846**, **BPC848**, **BPC850**, **BPC852**, **BPC858**, and **BPC860**.

These cyclic lipodepsipeptides were synthesized according to the protocol described in Scheme 4. After TFA cleavage, mass spectrometry analysis of the crude reaction mixtures showed the presence of the expected peptide along with a substantial amount of a byproduct with a m/z corresponding to $[M + H_2O]^+$. This byproduct could correspond to the linear precursor or to the linear compound resulting from the hydrolysis of the ester bond of the final cyclic depsipeptide. To verify the identity of this byproduct, the crude reaction mixtures were subjected to $CH_3OH/H_2O/NH_3$ (4:1:1).[40−42] As depicted in Scheme 5, if the linear precursor is present in the crudes, hydrolysis of the ester bond would lead to the release of the Ile residue (Scheme 5A). However, when the crudes were subjected to hydrolysis only peaks at $[M + H_2O]^+$ and at $[M + CH_3OH]^+$ were observed (Scheme 5B). This result demonstrated that the cyclizations were complete and that the cyclic lipodepsipeptides hydrolyzed during the cleavage or the HPLC analysis. The crude reaction mixtures from the synthesis of **BPC858** and **BPC860** were purified by reverse-phase column chromatography and were obtained in 78% and 70% HPLC purity, respectively.

In our previous studies on the synthesis of the macrolactone of eight amino acids present in fengycins, compounds bearing the same configuration at the Tyr residues as the cyclic lipodepsipeptides depicted in Figure 4 were obtained together with a dimeric product and the linear precursor prior to cyclization.[35] The results obtained herein point out, on one hand, that the presence of the fatty acid tail in the linear precursor may favor its cyclization and, on the other hand, that the resulting macrolactone is less stable than the one containing the Tyr residues with an opposite configuration (i.e., **BPC846** vs **BPC838**). Moreover, these findings further

Scheme 5. Hydrolysis Reaction of the Crude Reaction Mixtures from the Synthesis of the Cyclic Lipodepsipeptides: (A) Hydrolysis of the Linear Precursors; (B) Hydrolysis of the Cyclic Lipodepsipeptides



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support the recent hypothesis of Honma and co-workers that postulated L-Tyr[3]/D-Tyr[9] as the correct fengycin configuration.[19]

CONCLUSION

In summary, here we describe an efficient solid-phase approach for the total synthesis of dehydroxy derivatives of fengycins A, B, and S. The synthesis was accomplished using a Fmoc/^{t}Bu/allyl strategy, the key steps being the formation of a phenyl ester and the final macrolactamization. This study revealed the significance of the configuration of the Tyr residues on the stability of the macrolactone and showed that the most stable compounds were those containing an L-Tyr[3] and a D-Tyr[9]. This study represents the first approach on the total solid-phase synthesis of fengycin derivatives and would allow rapid access to a large variety of analogues.[43]

EXPERIMENTAL SECTION

General Methods. Peptide synthesis was performed manually in a polypropylene syringe fitted with a polyethylene porous disc. Solvents and soluble reagents were removed in vacuo. Wang resin was purchased from Fluka. Amino acid derivatives and other chemical reagents were purchased from IrisBiotech, Sigma-Aldrich, or Panreac and used without further purification, unless otherwise noted. Solvents were purchased from Sigma-Aldrich, Sharlau, VidraFoc, SDS, or VWR International. All organic solvents were synthesis grade except for CH_3CN, which was multisolvent HPLC grade. Solvents were purified and dried by an activated alumina purification system (mBraun SPS-800) or by conventional distillation techniques. H_2O was deionized and filtered by a COT Millipore Q-gradient system (COT < 3 ppb) with a resistivity of 18 MΩ·cm^{-1}.

Microwave-assisted reactions were carried out on a Discover S-Class CEM Corp. Microwave equipped with an Explorer-Autosampler and controlled with the Synergy software. The equipment was provided with a multispeed magnetic stirring system with adjustable speed and an automated power control system based on temperature feedback through a volume-independent noninvasive infrared sensor control which ranges from 0 to 300 W. The work temperature range is from 40 to 300 °C with a heating rate of 2−6 °C/s. The reactions were performed in 35 mL reaction vessels whose volume can range from 2 to 25 mL.

Compounds were analyzed under standard analytical high-performance liquid chromatography (HPLC) conditions using a Dionex liquid chromatography instrument composed of an UV/vis Dionex UVD170U detector, a P680 Dionex bomb, and an ASI-100 Dionex automatic injector and using the CHROMELEON 6.60 software. The analysis was carried out with a Kromasil 100 C_{18} (4.6 mm × 40 mm, 3.5 μm) column with a 2−100% B linear gradient over 7 min at a flow rate of 1 mL/min. Solvent A was 0.1% aq TFA, and solvent B was 0.1% TFA in CH_3CN. Detection was performed at 220 nm. Purity was estimated with the integrated area under peaks. Peptide purifications were carried on a reverse-phase column chromatography CombiFlash Rf200.

MS (ESI) were recorded with an Esquire 6000 ESI Bruker ion Trap LC/MS instrument equipped with an electrospray ion source (Serveis Tècnics de recerca, University of Girona). The instrument was operated in both positive ESI(+) and negative ESI(−) ion modes. Samples (5 μL) were introduced into the mass spectrometer ion source directly through a 1200 Series Agilent HPLC autosampler. The mobile phase (80:20 CH_3CN/H_2O at a flow rate of 100 μL/min) was delivered by an Agilent HPLC pump. Nitrogen was employed as both drying and nebulizing gas.

HRMS analyses were performed under conditions of ESI with a Bruker MicroTOF-QII instrument using a hybrid quadrupole time-of-flight mass spectrometer (Serveis Tècnics de Recerca, University of Girona). Samples were introduced into the mass spectrometer ion source by direct infusion through a syringe pump and were externally calibrated using sodium formate. The instrument was operated in positive ESI(+) ion mode.

NMR spectra (^{1}H NMR, ^{13}C NMR) were recorded with a 400 or 300 MHz Bruker Ultrashield Avance spectrometer. Chemical shifts were reported as δ values (ppm) directly referenced to undeuterated residual solvent signal (i.e., DMSO-d_6 δ = 2.50 ppm). The following multiplicity abbreviations are used: (d) doublet, (dd) double doublet, (td) triple doublet, (m) multiplet, and (br) broad peak. 2D-COSY and 2D-TOCSY experiments were carried out to assign the ^{1}H NMR peaks of the cyclic lipodepsipeptides.

IR spectra were recorded with a Bruker Alpha FT-IR spectrometer equipped with a Bruker platinum ATR adaptador, and wavenumbers (ν) are expressed in cm^{-1}.

The "&" symbol was used as an indicator of the ester chemical bond to facilitate the view of cyclic depsipeptide formulas. On the one-line formula, the "&" symbol indicates both the location of one end of a chemical bond and the point to which this bond is attached. This symbol has already been used in the nomenclature of other cyclic depsipeptides.[39]

Allyl N^α-(9-fluorenylmethyloxycarbonyl)-D-tyrosinate, allyl N^α-(9-fluorenylmethyloxycarbonyl)-L-tyrosinate, and N^α-allyloxycarbonyl-L-isoleucine were prepared according to previously reported procedures.[35]

Synthesis of Amino Acids. ***N^α-(p-Nitrobenzyloxycarbonyl)-O-tert-butyl-L-tyrosine.***[36] NaN_3 (164.37 mg, 2.53 mmol) was dissolved in H_2O (0.66 mL). and the mixture was added to a solution of *p*Nz-Cl (468.3 mL, 2.11 mmol) in 1,4-dioxane (0.92 mL). The mixture was stirred at room temperature for 2 h until the formation of *p*-nitrobenzylazidoformate (*p*Nz-N_3). Next, a solution of H-L-Tyr(^{t}Bu)-OH (500 mg, 2.11 mmol) in 1% Na_2CO_3/1,4-dioxane (1:1, 2.63 mL) was added dropwise. The resulting white suspension was stirred for 48 h at room temperature, keeping the pH between 8 and 10 by addition of 10% Na_2CO_3. The progress of the reaction was monitored by TLC. Once the reaction was completed, H_2O (30 mL) was added and the resulting suspension was washed with *tert*-butyl methyl ether (3 × 15 mL). The aqueous portion was acidified to pH 2 with 3 N HCl, and a precipitate appeared, which was filtered off and dried to yield *p*Nz-L-Tyr(^{t}Bu)-OH as a white solid (653.3 mg, 75% yield). ^{1}H NMR (400 MHz, CD_3OD) δ (ppm): 1.31 (s, 9H, $(CH_3)_3$), 2.87 (dd, *J* = 9.6, 14.0 Hz, 1H, CH_2-β), 3.20 (dd, *J* = 4.6, 14.0 Hz, 1H, CH_2-β), 4.39 (dd, *J* = 4.6, 9.6 Hz, 1H, CH-α), 5.09 (d, *J* = 13.8 Hz, 1H, OCH_2), 5.19 (d, *J* = 13.8 Hz, 1H, OCH_2), 6.88 (d, *J* = 8.6 Hz, 2H, CH_{Arom3}-Tyr), 7.14 (d, *J* = 8.6 Hz, 2H, CH_{Arom2}-Tyr), 7.45 (d, *J* = 8.8 Hz, 2H, CH_{Arom2}-*p*Nz), 8.20 (d, *J* = 8.8 Hz, 2H, CH_{Arom3}-*p*Nz). ^{13}C{^{1}H} NMR (400 MHz, CD_3OD) δ (ppm): 29.2 ($(CH_3)_3$), 38.3 (CH_2-β), 57.3 (CH-α), 65.9 (OCH_2), 79.4 ($C(CH_3)_3$), 124.5, 125.1 (CH_{Arom3}-Tyr, CH_{Arom3}-*p*Nz), 128.9, 130.9 (CH_{Arom2}-Tyr, CH_{Arom2}-*p*Nz), 133.9 (C_{Arom1}-Tyr), 146.1, 148.8 (C_{Arom1}-*p*Nz, C_{Arom4}-*p*Nz), 155.3 (OC_{Arom4}-Tyr), 157.8 (HN−C═O), 175.7 (COOH).

N^α-(p-Nitrobenzyloxycarbonyl)-L-tyrosine. This compound was prepared following the procedure described for Fmoc-L-Tyr-OAll starting from *p*Nz-L-Tyr(^{t}Bu)-OH (613.3 mg, 1.47 mmol). *p*Nz-L-Tyr-OH was obtained quantitatively as a white solid (478.1 mg, 90% yield). IR (neat): 3325 (COO-H_{st}), 1697 (C═O_{st}), 1608, 1512 ($NO_{2\ st\ as}$), 1441, 1343 ($NO_{2\ st\ sim}$), 1201, 1105, 1059 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ (ppm): 2.82 (dd, *J* = 9.6, 14.0 Hz, 1H, CH_2-β), 3.13 (dd, *J* = 4.8, 14.0 Hz, 1H, CH_2-β), 4.38 (dd, *J* = 4.8, 9.6 Hz, 1H, CH-α), 5.11 (d, *J* = 14.0 Hz, 1H, OCH_2), 5.19 (d, *J* = 14.0 Hz, 1H, OCH_2), 6.70 (d, *J* = 8.4 Hz, 2H, CH_{Arom3}-Tyr), 7.05 (d, *J* = 8.4 Hz, 2H, CH_{Arom2}-Tyr), 7.45 (d, *J* = 8.8 Hz, 2H, CH_{Arom2}-*p*Nz), 8.19 (d, *J* = 8.8 Hz, 2H, CH_{Arom3}-*p*Nz). ^{13}C{^{1}H} NMR (400 MHz, CD_3OD) δ (ppm): 37.9 (CH_2-β), 57.0 (CH-α), 66.0 (OCH_2), 116.2 (CH_{Arom3}-Tyr), 124.5 (CH_{Arom3}-*p*Nz), 128.8, 129.2 (CH_{Arom2}-Tyr, CH_{Arom2}-*p*Nz), 131.3 (C_{Arom1}-Tyr), 146.1, 148.8 (C_{Arom1}-*p*Nz, C_{Arom4}-*p*Nz), 157.3, 157.9 (OC_{Arom4}-Tyr, HN−C═O), 175.2 (COOH). MS (ESI) *m/z*: 361.0 $[M + H]^+$, 383.0 $[M + Na]^+$.

N^α-(9-Fluorenylmethyloxycarbonyl)-D-tyrosine. The commercial amino acid Fmoc-D-Tyr(O^{t}Bu)-OH (0.6 g, 1.31 mmol) was dissolved in TFA/CH_2Cl_2 (1:1) and stirred at room temperature for 3 h. The solution was concentrated to dryness followed by repeated washings

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and evaporations with diethyl ether. The resulting residue was digested in pentane to yield Fmoc-D-Tyr-OH as a white powder (0.58 g, 97% yield). IR (neat): 3308 (OH_{st}), 1685 ($C{=}O_{st}$), 1541, 1515 (arC-C_{st}, NH_{δ}), 1450 ($CH_{2\delta}$), 1230 (arC-O_{st}), 735 ($CH_{2\gamma}$) cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.74 (dd, J = 10.8, 13.6 Hz, 1H, CH_2-β), 2.95 (dd, J = 4.0, 13.6 Hz, 1H, CH_2-β), 4.05−4.11 (m, 1H, CH-Fmoc), 4.15−4.21 (m, 3H, OCH_2-Fmoc, CH-α), 6.66 (d, J = 8.4 Hz, 2H, CH_{Arom6}-Tyr), 7.06 (d, J = 8.4 Hz, 2H, CH_{Arom5}-Tyr), 7.27−7.34 (m, 2H, CH_{Arom13}-Fmoc), 7.41 (td, J = 3.2, 7.6 Hz, 2H, CH_{Arom14}-Fmoc), 7.63−7.71 (m, 3H, CH_{Arom12}-Fmoc, OH), 7.88 (d, J = 7.6 Hz, 2H, CH_{Arom15}-Fmoc) 9.22 (br, 1H, NH), 12.71 (br, 1H, COOH). $^{13}C\{^1H\}$ NMR (300 MHz, DMSO-d_6) δ (ppm): 35.2 (CH_2-β), 46.1 (CH-Fmoc), 55.4 (CH-α), 65.1 (OCH_2-Fmoc), 114.5 (CH_{Arom6}-Tyr), 119.6, 124.8, 126.6, 127.1, 127.5 (CH_{Arom12}-Fmoc, CH_{Arom13}-Fmoc, CH_{Arom14}-Fmoc, CH_{Arom15}-Fmoc, $C_{q\text{-}Arom4}$-Tyr), 129.5 (CH_{Arom5}-Tyr), 140.2, 143.2 ($C_{q\text{-}Arom11}$-Fmoc, $C_{q\text{-}Arom16}$-Fmoc), 155.4, 155.4 ($OC_{q\text{-}Arom7}$-Tyr, NH−C=O), 173.0 (O−C=O). MS (ESI) m/z: 404.0 $[M + H]^+$, 426.1 $[M + Na]^+$.

N^α-(9-Fluorenylmethyloxycarbonyl)-L-tyrosine. Starting from the commercially available Fmoc-L-Tyr(O^{t}Bu)-OH (0.5 g, 1.09 mmol), this compound was prepared following the procedure described above for Fmoc-D-Tyr-OH. Fmoc-L-Tyr-OH was obtained as a white powder (0.43 g, 96% yield). IR (neat): 3354 (OH_{st}), 1655 ($C{=}O_{st}$), 1538, 1514 (arC-C_{st}, NH_{δ}), 1449 ($CH_{2\delta}$), 1256, 1220 (arC-O_{st}), 735 ($CH_{2\gamma}$) cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.75 (dd, J = 10.4, 13.8 Hz, 1H, CH_2-β), 2.95 (dd, J = 4.4, 13.8 Hz, 1H, CH_2-β), 4.05−4.11 (m, 1H, CH-Fmoc), 4.15−4.22 (m, 3H, OCH_2-Fmoc, CH-α), 6.66 (d, J = 8.4 Hz, 2H, CH_{Arom6}-Tyr), 7.06 (d, J = 8.4 Hz, 2H, CH_{Arom5}-Tyr), 7.27−7.34 (m, 2H, CH_{Arom13}-Fmoc), 7.39−7.43 (m, 2H, CH_{Arom14}-Fmoc), 7.63−7.68 (m, 3H, CH_{Arom12}-Fmoc, OH), 7.88 (d, J = 7.2 Hz, 2H, CH_{Arom15}-Fmoc), 9.20 (br, 1H, NH), 12.68 (br, 1H, COOH). $^{13}C\{^1H\}$ NMR (400 MHz, DMSO-d_6) δ (ppm): 36.2 (CH_2-β), 47.0 (CH-Fmoc), 56.3 (CH-α), 66.1 (OCH_2-Fmoc), 115.4 (CH_{Arom6}-Tyr), 120.5, 125.7, 127.5, 128.1, 128.4 (CH_{Arom12}-Fmoc, CH_{Arom13}-Fmoc, CH_{Arom14}-Fmoc, CH_{Arom15}-Fmoc, $C_{q\text{-}Arom4}$-Tyr), 130.48 (CH_{Arom5}-Tyr), 141.1, 144.2 ($C_{q\text{-}Arom11}$-Fmoc, $C_{q\text{-}Arom16}$-Fmoc), 156.3, 156.4 ($OC_{q\text{-}Arom7}$-Tyr, NH−C=O), 173.9 (O−C=O). MS (ESI) m/z: 404.0 $[M + H]^+$, 426.1 $[M + Na]^+$.

Solid-Phase Synthesis of Cyclic Lipodepsipeptides. *Synthesis of Peptidyl Resins **1** and **6** and of the Linear Lipopeptidyl Resins.* Wang resin (450 mg, loading 1.1 mmol/g, 100−200 mesh, cross-linked with 1% DVB) was placed in a microwave tube and swollen in dry tetrahydrofuran (THF) for 30 min. A solution of Fmoc-L-Tyr-OAll or Fmoc-D-Tyr-OAll (878.11 mg, 1.98 mmol) and triphenylphosphine (PPh_3) (519.35 mg, 1.98 mmol) in dry THF (3 mL) was added to the resin, and the resulting mixture was cooled at 0 °C. A solution of diisopropylazodicarboxylate (DIAD, 390 μL, 1.98 mmol) in dry THF (0.5 mL) was added dropwise, and the mixture was stirred 1 h at 0 °C. The resulting mixture was subjected to microwave irradiaton at 60 °C for 30 min. Then the resin was transferred to a polypropylene syringe and washed sequentially with THF (3 × 2 min), CH_2Cl_2 (3 × 2 min), DMF (3 × 2 min), DMF/H_2O (1:1, 3 × 2 min), DMF (3 × 2 min), CH_3OH (3 × 2 min), CH_2Cl_2 (3 × 2 min), and diethyl ether (3 × 2 min) and dried in vacuo. The loading of the resulting resins Fmoc-L-Tyr(Wang)-OAll and Fmoc-D-Tyr(Wang)-OAll was determined using the Fmoc test, being 0.20 and 0.29 mmol/g, respectively.[37] The racemization of the anchored amino acid was evaluated using Marfey's reagent.[38] Finally, the resin was acetylated with acetic anhydride/pyridine/CH_2Cl_2 (86:7:7, 2 × 30 min). The resin was washed with CH_2Cl_2 (3 × 2 min), DMF (3 × 2 min), CH_3OH (3 × 1 min), CH_2Cl_2 (3 × 2 min), and diethyl ether (3 × 2 min) and dried in vacuo.[44]

Fmoc-L-Tyr(Wang)-OAll and Fmoc-D-Tyr(Wang)-OAll resins were elongated by the solid-phase method following a standard Fmoc chemistry. Fmoc-Gln(Tr)-OH, Fmoc-Pro-OH, Fmoc-D-Val-OH, Fmoc-D-Ala-OH, Fmoc-Glu(O^{t}Bu)-OH, Fmoc-D-Thr(^{t}Bu)-OH, Fmoc-D-Ser(^{t}Bu)-OH, Fmoc-Tyr-OH, Fmoc-D-Tyr-OH, Fmoc-D-Orn(Boc)-OH, and pNZ-Tyr-OH were used as amino acid derivatives. The coupling of the corresponding protected amino acid (4 equiv) was carried out in the presence of ethyl 2-cyano-2-(hydroxyimino) acetate (Oxyma) (4 equiv) and N,N'-diisopropylcarbodiimide (DIPCDI) (4 equiv) in DMF for 3 h under stirring at room temperature. The completion of each coupling was monitored by a Kaiser test[45] or a chloranil test.[46] The Fmoc protecting group was removed by treating the resin with piperidine/DMF (3:7, 1 × 2 + 3 × 10 min). After each coupling and deprotection step, the resin was washed with DMF (6 × 1 min) and CH_2Cl_2 (3 × 1 min) and air dried.

To obtain the lipopeptidyl resins, each peptidyl resin was subjected to N-terminal Fmoc removal as described above. After washings, the resin was treated with the corresponding fatty acid (3 equiv), Oxyma (3 equiv), and DIPCDI (3 equiv) in DMF under overnight stirring at room temperature. The resin was then washed with DMF (6 × 1 min) and CH_2Cl_2 (3 × 1 min) and air dried. Completion of the reaction was checked with the Kaiser test.[45] An aliquot of each resulting lipopeptidyl resin was treated with trifluoroacetic acid (TFA)/H_2O/triisopropylsilane (TIS) (95:2.5:2.5) for 2 h at room temperature. Following TFA evaporation, the resulting crude lipopeptide was precipitated with diethyl ether and then decanted to give a white solid that was taken up in H_2O/CH_3CN (1:1), lyophilized, and analyzed by HPLC and mass spectrometry.

*Linear Peptidyl Resin pNZ-Tyr-D-Thr(^{t}Bu)-Glu(O^{t}Bu)-D-Val-Pro-Gln(Tr)-D-Tyr(Wang)-OAll (**1**).* Starting from Fmoc-D-Tyr(Wang)-OAll, this peptidyl resin was prepared following the above general procedure. Acidolytic cleavage of an aliquot of **1** afforded pNZ-Tyr-D-Thr-Glu-D-Val-Pro-Gln-D-Tyr-OAll in 65% purity. HPLC (λ = 220 nm) t_R = 7.28 min. MS (ESI) $m/z(+)$: 1118.5 $[M + H]^+$, 1140.4 $[M + Na]^+$, 1156.4 $[M + K]^+$.

*Linear Peptidyl Resin Fmoc-Glu(O^{t}Bu)-D-Orn(Boc)-Tyr-D-Thr(^{t}Bu)-Glu(O^{t}Bu)-D-Val-Pro-Gln(Tr)-D-Tyr(Wang)-OAll (**6**).* Starting from Fmoc-D-Tyr(Wang)-OAll, this peptidyl resin was prepared following the above general procedure. Acidolytic cleavage of an aliquot of **1** afforded Fmoc-Glu-D-Orn-Tyr-D-Thr-Glu-D-Val-Pro-Gln-D-Tyr-OAll in 74% purity. HPLC (λ = 220 nm) t_R = 7.23 min.

*Linear Lipopeptidyl Resin C_7H_{15}CO-Glu(O^{t}Bu)-D-Orn(Boc)-Tyr-D-Thr(^{t}Bu)-Glu(O^{t}Bu)-D-Val-Pro-Gln(Tr)-D-Tyr(Wang)-OAll (**5a**).* This peptidyl resin was prepared from **6** following the above procedure using octanoic acid as fatty acid. Acidolytic cleavage of an aliquot of **5a** afforded C_7H_{15}CO-Glu-D-Orn-Tyr-D-Thr-Glu-D-Val-Pro-Gln-D-Tyr-OAll in 79% purity. HPLC (λ = 220 nm) t_R = 7.09 min. MS (ESI) $m/z(+)$: 654.8 $[M + 2H]^{2+}$, 1308.7 $[M + H]^+$, 1330.6 $[M + Na]^+$. MS (ESI) $m/z(-)$: 1306.7 $[M - H]^-$, 1328.6 $[M + Na - 2H]^-$.

*Linear Lipopeptidyl Resin $C_{11}H_{23}$CO-Glu(O^{t}Bu)-D-Orn(Boc)-Tyr-D-Thr(^{t}Bu)-Glu(O^{t}Bu)-D-Val-Pro-Gln(Tr)-D-Tyr(Wang)-OAll (**5b**).* This peptidyl resin was prepared from **6** following the above procedure using lauric acid as fatty acid. Acidolytic cleavage of an aliquot of **5b** afforded $C_{11}H_{23}$CO-Glu-D-Orn-Tyr-D-Thr-Glu-D-Val-Pro-Gln-D-Tyr-OAll in 90% purity. HPLC (λ = 220 nm) t_R = 7.91 min. MS (ESI) $m/z(+)$: 683.3 $[M + 2H]^{2+}$, 1364.8 $[M + H]^+$. MS (ESI) $m/z(-)$: 1362.7 $[M - H]^-$, 1384.6 $[M + Na - 2H]^-$.

*Linear Lipopeptidyl Resin $C_{15}H_{31}$CO-Glu(O^{t}Bu)-D-Orn(Boc)-Tyr-D-Thr(^{t}Bu)-Glu(O^{t}Bu)-D-Val-Pro-Gln(Tr)-D-Tyr(Wang)-OAll (**5c**).* This peptidyl resin was prepared from **6** following the above procedure using palmitic acid as fatty acid. Acidolytic cleavage of an aliquot of **5c** afforded $C_{15}H_{31}$CO-Glu-D-Orn-Tyr-D-Thr-Glu-D-Val-Pro-Gln-D-Tyr-OAll in 93% purity. HPLC (λ = 220 nm) t_R = 8.84 min. MS (ESI) $m/z(+)$: 1420.8 $[M + H]^+$. MS (ESI) $m/z(-)$: 1418.7 $[M - H]^-$, 1440.7 $[M + Na - 2H]^-$.

Linear Lipopeptidyl Resin C_7H_{15}CO-Glu(O^{t}Bu)-D-Orn(Boc)-Tyr-D-Ser(^{t}Bu)-Glu(O^{t}Bu)-D-Val-Pro-Gln(Tr)-D-Tyr(Wang)-OAll. Starting from Fmoc-D-Tyr(Wang)-OAll, this peptidyl resin was prepared following the above general procedure using octanoic acid as fatty acid. Acidolytic cleavage of an aliquot of the resulting resin afforded C_7H_{15}CO-Glu-D-Orn-Tyr-D-Ser-Glu-D-Val-Pro-Gln-D-Tyr-OAll in 67% purity. HPLC (λ = 220 nm) t_R = 6.97 min. MS (ESI) $m/z(+)$: 647.8 $[M + 2H]^{2+}$, 1294.6 $[M + H]^+$. MS (ESI) $m/z(-)$: 1292.6 $[M - H]^-$, 1314.5 $[M + Na - 2H]^-$.

Linear Lipopeptidyl Resin C_7H_{15}CO-Glu(O^{t}Bu)-D-Orn(Boc)-Tyr-D-Thr(^{t}Bu)-Glu(O^{t}Bu)-D-Ala-Pro-Gln(Tr)-D-Tyr(Wang)-OAll. Starting

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from Fmoc-D-Tyr(Wang)-OAll, this peptidyl resin was prepared following the above general procedure using octanoic acid as fatty acid. Acidolytic cleavage of an aliquot of the resulting resin afforded C_7H_{15}CO-Glu-D-Orn-Tyr-D-Thr-Glu-D-Ala-Pro-Gln-D-Tyr-OAll in 64% purity. HPLC (λ = 220 nm) t_R = 6.89 min. MS (ESI) $m/z(+)$: 641.3 $[M + 2H]^{2+}$, 1280.6 $[M + H]^+$. MS (ESI) $m/z(-)$: 1278.6 $[M - H]^-$, 1300.5 $[M + Na - 2H]^-$.

Linear Lipopeptidyl Resin C_7H_{15}CO-Glu(O^{t}Bu)-D-Orn(Boc)-Tyr-D-Ser(^{t}Bu)-Glu(O^{t}Bu)-D-Ala-Pro-Gln(Tr)-D-Tyr(Wang)-OAll. Starting from Fmoc-D-Tyr(Wang)-OAll, this peptidyl resin was prepared following the above general procedure using octanoic acid as fatty acid. Acidolytic cleavage of an aliquot of the resulting resin afforded C_7H_{15}CO-Glu-D-Orn-Tyr-D-Ser-Glu-D-Ala-Pro-Gln-D-Tyr-OAll in 71% purity. HPLC (λ = 220 nm) t_R = 6.84 min. MS (ESI) $m/z(+)$: 633.7 $[M + 2H]^{2+}$, 1266.6 $[M + H]^+$. MS (ESI) $m/z(-)$: 1264.6 $[M - H]^-$, 1286.5 $[M + Na - 2H]^-$.

Linear Lipopeptidyl Resin C_7H_{15}CO-Glu(O^{t}Bu)-D-Orn(Boc)-D-Tyr-D-Thr(^{t}Bu)-Glu(O^{t}Bu)-D-Val-Pro-Gln(Tr)-Tyr(Wang)-OAll. Starting from Fmoc-Tyr(Wang)-OAll, this peptidyl resin was prepared following the above general procedure using octanoic acid as fatty acid. Acidolytic cleavage of an aliquot of the resulting resin afforded C_7H_{15}CO-Glu-D-Orn-D-Tyr-D-Thr-Glu-D-Val-Pro-Gln-Tyr-OAll in 69% purity. HPLC (λ = 220 nm) t_R = 7.00 min. MS (ESI) $m/z(+)$: 1308.6 $[M + H]^+$. MS (ESI) $m/z(-)$: 1306.6 $[M - H]^-$.

Linear Lipopeptidyl Resin C_7H_{15}CO-Glu(O^{t}Bu)-D-Orn(Boc)-D-Tyr-D-Ser(^{t}Bu)-Glu(O^{t}Bu)-D-Val-Pro-Gln(Tr)-Tyr(Wang)-OAll. Starting from Fmoc-Tyr(Wang)-OAll, this peptidyl resin was prepared following the above general procedure using octanoic acid as fatty acid. Acidolytic cleavage of an aliquot of the resulting resin afforded C_7H_{15}CO-Glu-D-Orn-D-Tyr-D-Ser-Glu-D-Val-Pro-Gln-Tyr-OAll in 67% purity. HPLC (λ = 220 nm) t_R = 6.97 min. MS (ESI) $m/z(+)$: 647.7 $[M + 2H]^{2+}$, 1294.6 $[M + H]^+$, 1316.6 $[M + Na]^+$. MS (ESI) $m/z(-)$: 1292.6 $[M - H]^-$, 1314.5 $[M + Na - 2H]^-$.

Linear Lipopeptidyl Resin C_7H_{15}CO-Glu(O^{t}Bu)-D-Orn(Boc)-D-Tyr-D-Thr(^{t}Bu)-Glu(O^{t}Bu)-D-Ala-Pro-Gln(Tr)-Tyr(Wang)-OAll. Starting from Fmoc-Tyr(Wang)-OAll, this peptidyl resin was prepared following the above general procedure using octanoic acid as fatty acid. Acidolytic cleavage of an aliquot of the resulting resin afforded C_7H_{15}CO-Glu-D-Orn-D-Tyr-D-Thr-Glu-D-Ala-Pro-Gln-Tyr-OAll in 68% purity. HPLC (λ = 220 nm) t_R = 6.89 min. MS (ESI) $m/z(+)$: 1280.6 $[M + H]^+$, 1302.6 $[M + Na]^+$. MS (ESI) $m/z(-)$: 1278.6 $[M - H]^-$, 1300.5 $[M + Na - 2H]^-$.

Linear Lipopeptidyl Resin C_7H_{15}CO-Glu(O^{t}Bu)-D-Orn(Boc)-D-Tyr-D-Ser(^{t}Bu)-Glu(O^{t}Bu)-D-Ala-Pro-Gln(Tr)-Tyr(Wang)-OAll. Starting from Fmoc-Tyr(Wang)-OAll, this peptidyl resin was prepared following the above general procedure using octanoic acid as fatty acid. Acidolytic cleavage of an aliquot of the resulting resin afforded C_7H_{15}CO-Glu-D-Orn-D-Tyr-D-Ser-Glu-D-Ala-Pro-Gln-Tyr-OAll in 67% purity. HPLC (λ = 220 nm) t_R = 6.85 min. MS (ESI) $m/z(+)$: 1266.6 $[M + H]^+$, 1288.6 $[M + Na]^+$. MS (ESI) $m/z(-)$: 1264.6 $[M - H]^-$, 1286.5 $[M + Na - 2H]^-$.

Linear Lipopeptidyl Resin $C_{11}H_{23}$CO-Glu(O^{t}Bu)-D-Orn(Boc)-D-Tyr-D-Thr(^{t}Bu)-Glu(O^{t}Bu)-D-Val-Pro-Gln(Tr)-Tyr(Wang)-OAll. Starting from Fmoc-Tyr(Wang)-OAll, this peptidyl resin was prepared following the above general procedure using lauric acid as fatty acid. Acidolytic cleavage of an aliquot of the resulting resin afforded $C_{11}H_{23}$CO-Glu-D-Orn-D-Tyr-D-Thr-Glu-D-Val-Pro-Gln-Tyr-OAll in 66% purity. HPLC (λ = 220 nm) t_R = 8.14 min. MS (ESI) $m/z(+)$: 1364.7 $[M + H]^+$, 1386.7 $[M + Na]^+$. MS (ESI) $m/z(-)$: 1362.7 $[M - H]^-$, 1384.6 $[M + Na - 2H]^-$.

Linear Lipopeptidyl Resin $C_{15}H_{31}$CO-Glu(O^{t}Bu)-D-Orn(Boc)-D-Tyr-D-Thr(^{t}Bu)-Glu(O^{t}Bu)-D-Val-Pro-Gln(Tr)-Tyr(Wang)-OAll. Starting from Fmoc-Tyr(Wang)-OAll, this peptidyl resin was prepared following the above general procedure using palmitic acid as fatty acid. Acidolytic cleavage of an aliquot of the resulting resin afforded $C_{15}H_{31}$CO-Glu-D-Orn-D-Tyr-D-Thr-Glu-D-Val-Pro-Gln-Tyr-OAll in 79% purity. HPLC (λ = 220 nm) t_R = 9.11 min. MS (ESI) $m/z(+)$: 710.8 $[M + 2H]^{2+}$, 1420.8 $[M + H]^+$, 1442.8 $[M + Na]^+$. MS (ESI) $m/z(-)$: 708.8 $[M - 2H]^{2-}$, 1418.7 $[M - H]^-$, 1440.7 $[M + Na - 2H]^-$.

Synthesis of Linear Depsipeptidyl Resins Containing a Phenyl Ester. Each peptidyl resin was treated with Alloc-L-Ile-OH (7 equiv), DIEA (1.4 equiv), DIPCDI (7 equiv), and DMAP (0.7 equiv) in DMF for 24 h at room temperature. This treatment was repeated twice. After each treatment, the resin was washed with DMF (6 × 1 min) and CH_2Cl_2 (3 × 1 min) and air dried. An aliquot of the each resulting resin was treated with TFA/H_2O/TIS (95:2.5:2.5) for 2 h at room temperature. Following TFA evaporation and diethyl ether extraction, the crude peptide was dissolved in H_2O/CH_3CN, lyophilized, analyzed by HPLC, and characterized by mass spectrometry.

*Linear Depsipeptidyl Resin pNZ-Tyr(O-Ile-Alloc)-D-Thr(^{t}Bu)-Glu(O^{t}Bu)-D-Val-Pro-Gln(Tr)-D-Tyr(Wang)-OAll (**2**).* Starting from **1**, this depsipeptidyl resin was prepared according to the general procedure described above. Acidolytic cleavage of an aliquot of **2** afforded *p*NZ-Tyr(O-Ile-Alloc)-D-Thr-Glu-D-Val-Pro-Gln-D-Tyr-OAll in 87% purity. HPLC (λ = 220 nm) t_R = 8.21 min. MS (ESI) $m/z(+)$: 1315.6 $[M + H]^+$, 1337.6 $[M + Na]^+$, 1353.5 $[M + K]^+$.

*Linear Lipodepsipeptidyl Resin C_7H_{15}CO-Glu(O^{t}Bu)-D-Orn(Boc)-Tyr(O-Ile-Alloc)-D-Thr(^{t}Bu)-Glu(O^{t}Bu)-D-Val-Pro-Gln(Tr)-D-Tyr-(Wang)-OAll (**7a**).* Starting from **5a**, this depsipeptidyl resin was prepared according to the general procedure described above. Acidolytic cleavage of an aliquot of **7a** afforded C_7H_{15}CO-Glu-D-Orn-Tyr(O-Ile-Alloc)-D-Thr-Glu-D-Val-Pro-Gln-D-Tyr-OAll in 81% purity. HPLC (λ = 220 nm) t_R = 7.82 min. MS (ESI) $m/z(+)$: 753.3 $[M + 2H]^{2+}$, 1505.7 $[M + H]^+$. MS (ESI) $m/z(-)$: 1503.7 $[M - H]^-$, 1525.6 $[M + Na - 2H]^-$.

*Linear Lipodepsipeptidyl Resin $C_{11}H_{23}$CO-Glu(O^{t}Bu)-D-Orn(Boc)-Tyr(O-Ile-Alloc)-D-Thr(^{t}Bu)-Glu(O^{t}Bu)-D-Val-Pro-Gln(Tr)-D-Tyr-(Wang)-OAll (**7b**).* Starting from **5b**, this depsipeptidyl resin was prepared according to the general procedure described above. Acidolytic cleavage of an aliquot of **7b** afforded $C_{11}H_{23}$CO-Glu-D-Orn-Tyr(O-Ile-Alloc)-D-Thr-Glu-D-Val-Pro-Gln-D-Tyr-OAll in 88% purity. HPLC (λ = 220 nm) t_R= 8.72 min. MS (ESI) $m/z(+)$: 781.4 $[M + 2H]^{2+}$, 1561.9 $[M + H]^+$. MS (ESI) $m/z(-)$: 1559.8 $[M - H]^-$, 1581.7 $[M + Na - 2H]^-$.

*Linear Lipodepsipeptidyl Resin $C_{15}H_{31}$CO-Glu(O^{t}Bu)-D-Orn(Boc)-Tyr(O-Ile-Alloc)-D-Thr(^{t}Bu)-Glu(O^{t}Bu)-D-Val-Pro-Gln(Tr)-D-Tyr-(Wang)-OAll (**7c**).* Starting from **5c**, this depsipeptidyl resin was prepared according to the general procedure described above. Acidolytic cleavage of an aliquot of **7c** afforded $C_{15}H_{31}$CO-Glu-D-Orn-Tyr(O-Ile-Alloc)-D-Thr-Glu-D-Val-Pro-Gln-D-Tyr-OAll in 88% purity. HPLC (λ = 220 nm) t_R= 9.74 min. MS (ESI) $m/z(+)$: 809.5 $[M + 2H]^{2+}$, 1617.9 $[M + H]^+$. MS (ESI) $m/z(-)$: 1615.8 $[M - H]^-$, 1637.8 $[M + Na - 2H]^-$.

Linear Lipodepsipeptidyl Resin C_7H_{15}CO-Glu(O^{t}Bu)-D-Orn(Boc)-Tyr(O-Ile-Alloc)-D-Ser(^{t}Bu)-Glu(O^{t}Bu)-D-Val-Pro-Gln(Tr)-D-Tyr-(Wang)-OAll. Starting from C_7H_{15}CO-Glu(O^{t}Bu)-D-Orn(Boc)-Tyr-D-Ser(^{t}Bu)-Glu(O^{t}Bu)-D-Val-Pro-Gln(Tr)-D-Tyr(Wang)-OAll, this depsipeptidyl resin was prepared according to the general procedure described above. Acidolytic cleavage of an aliquot of the resulting resin afforded C_7H_{15}CO-Glu-D-Orn-Tyr(O-Ile-Alloc)-D-Ser-Glu-D-Val-Pro-Gln-D-Tyr-OAll in 81% purity. HPLC (λ = 220 nm) t_R = 7.72 min. MS (ESI) $m/z(+)$: 746.3 $[M + 2H]^{2+}$, 1491.7 $[M + H]^+$. MS (ESI) $m/z(-)$: 1489.7 $[M - H]^-$, 1512.6 $[M + Na - 2H]^-$.

Linear Lipodepsipeptidyl Resin C_7H_{15}CO-Glu(O^{t}Bu)-D-Orn(Boc)-Tyr(O-Ile-Alloc)-D-Thr(^{t}Bu)-Glu(O^{t}Bu)-D-Ala-Pro-Gln(Tr)-D-Tyr-(Wang)-OAll. Starting from C_7H_{15}CO-Glu(O^{t}Bu)-D-Orn(Boc)-Tyr-D-Thr(^{t}Bu)-Glu(O^{t}Bu)-D-Ala-Pro-Gln(Tr)-D-Tyr(Wang)-OAll, this depsipeptidyl resin was prepared according to the general procedure described above. Acidolytic cleavage of an aliquot of the resulting resin afforded C_7H_{15}CO-Glu-D-Orn-Tyr(O-Ile-Alloc)-D-Thr-Glu-D-Ala-Pro-Gln-D-Tyr-OAll in 77% purity. HPLC (λ = 220 nm) t_R = 7.68 min. MS (ESI) $m/z(+)$: 739.8 $[M + 2H]^{2+}$, 1477.7 $[M + H]^+$. MS (ESI) $m/z(-)$: 1475.6 $[M - H]^-$, 1497.6 $[M + Na - 2H]^-$.

Linear Lipodepsipeptidyl Resin C_7H_{15}CO-Glu(O^{t}Bu)-D-Orn(Boc)-Tyr(O-Ile-Alloc)-D-Ser(^{t}Bu)-Glu(O^{t}Bu)-D-Ala-Pro-Gln(Tr)-D-Tyr-(Wang)-OAll. Starting from C_7H_{15}CO-Glu(O^{t}Bu)-D-Orn(Boc)-Tyr-D-Ser(^{t}Bu)-Glu(O^{t}Bu)-D-Ala-Pro-Gln(Tr)-D-Tyr(Wang)-OAll, this depsipeptidyl resin was prepared according to the general procedure described above. Acidolytic cleavage of an aliquot of the resulting

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resin afforded C_7H_{15}CO-Glu-D-Orn-Tyr(O-Ile-Alloc)-D-Ser-Glu-D-Ala-Pro-Gln-D-Tyr-OAll in 77% purity. HPLC (λ = 220 nm) t_R = 7.60 min. MS (ESI) $m/z(+)$: 732.3 $[M + 2H]^{2+}$, 1463.7 $[M + H]^{+}$. MS (ESI) $m/z(-)$: 1461.6 $[M - H]^{-}$, 1483.6 $[M + Na - 2H]^{-}$.

Linear Lipodepsipeptidyl Resin C_7H_{15}CO-Glu(O^{t}Bu)-D-Orn(Boc)-D-Tyr(O-Ile-Alloc)-D-Thr(^{t}Bu)-Glu(O^{t}Bu)-D-Val-Pro-Gln(Tr)-Tyr(Wang)-OAll. Starting from C_7H_{15}CO-Glu(O^{t}Bu)-D-Orn(Boc)-D-Tyr-D-Thr-(^{t}Bu)-Glu(O^{t}Bu)-D-Val-Pro-Gln(Tr)-Tyr(Wang)-OAll, this depsipeptidyl resin was prepared according to the general procedure described above. Acidolytic cleavage of an aliquot of the resulting resin afforded C_7H_{15}CO-Glu-D-Orn-D-Tyr(O-Ile-Alloc)-D-Thr-Glu-D-Val-Pro-Gln-Tyr-OAll in 79% purity. HPLC (λ = 220 nm) t_R = 7.94 min. MS (ESI) $m/z(+)$: 753.8 $[M + 2H]^{2+}$, 1505.8 $[M + H]^{+}$. MS (ESI) $m/z(-)$: 1503.7 $[M - H]^{-}$, 1526.7 $[M + Na - 2H]^{-}$.

Linear Lipodepsipeptidyl Resin C_7H_{15}CO-Glu(O^{t}Bu)-D-Orn(Boc)-D-Tyr(O-Ile-Alloc)-D-Ser(^{t}Bu)-Glu(O^{t}Bu)-D-Val-Pro-Gln(Tr)-Tyr(Wang)-OAll. Starting from C_7H_{15}CO-Glu(O^{t}Bu)-D-Orn(Boc)-D-Tyr-D-Ser-(^{t}Bu)-Glu(O^{t}Bu)-D-Val-Pro-Gln(Tr)-Tyr(Wang)-OAll, this depsipeptidyl resin was prepared according to the general procedure described above. Acidolytic cleavage of an aliquot of the resulting resin afforded C_7H_{15}CO-Glu-D-Orn-D-Tyr(O-Ile-Alloc)-D-Ser-Glu-D-Val-Pro-Gln-Tyr-OAll in 77% purity. HPLC (λ = 220 nm) t_R = 7.89 min. MS (ESI) $m/z(+)$: 746.3 $[M + 2H]^{2+}$, 1491.7 $[M + H]^{+}$. MS (ESI) $m/z(-)$: 1489.7 $[M - H]^{-}$, 1511.7 $[M + Na - 2H]^{-}$.

Linear Lipodepsipeptidyl Resin C_7H_{15}CO-Glu(O^{t}Bu)-D-Orn(Boc)-D-Tyr(O-Ile-Alloc)-D-Thr(^{t}Bu)-Glu(O^{t}Bu)-D-Ala-Pro-Gln(Tr)-Tyr(Wang)-OAll. Starting from C_7H_{15}CO-Glu(O^{t}Bu)-D-Orn(Boc)-D-Tyr-D-Thr-(^{t}Bu)-Glu(O^{t}Bu)-D-Ala-Pro-Gln(Tr)-Tyr(Wang)-OAll, this depsipeptidyl resin was prepared according to the general procedure described above. Acidolytic cleavage of an aliquot of the resulting resin afforded C_7H_{15}CO-Glu-D-Orn-D-Tyr(O-Ile-Alloc)-D-Thr-Glu-D-Ala-Pro-Gln-Tyr-OAll in 83% purity. HPLC (λ = 220 nm) t_R = 7.85 min. MS (ESI) $m/z(+)$: 739.8 $[M + 2H]^{2+}$, 1477.7 $[M + H]^{+}$. MS (ESI) $m/z(-)$: 1475.7 $[M - H]^{-}$, 1498.6 $[M + Na - 2H]^{-}$.

Linear Lipodepsipeptidyl Resin C_7H_{15}CO-Glu(O^{t}Bu)-D-Orn(Boc)-D-Tyr(O-Ile-Alloc)-D-Ser(^{t}Bu)-Glu(O^{t}Bu)-D-Ala-Pro-Gln(Tr)-Tyr(Wang)-OAll. Starting from C_7H_{15}CO-Glu(O^{t}Bu)-D-Orn(Boc)-D-Tyr-D-Ser-(^{t}Bu)-Glu(O^{t}Bu)-D-Ala-Pro-Gln(Tr)-Tyr(Wang)-OAll, this depsipeptidyl resin was prepared according to the general procedure described above. Acidolytic cleavage of an aliquot of the resulting peptidyl resin afforded C_7H_{15}CO-Glu-D-Orn-D-Tyr(O-Ile-Alloc)-D-Ser-Glu-D-Ala-Pro-Gln-Tyr-OAll in 83% purity. HPLC (λ = 220 nm) t_R = 7.79 min. MS (ESI) $m/z(+)$: 732.3 $[M + 2H]^{2+}$, 1463.7 $[M + H]^{+}$. MS (ESI) $m/z(-)$: 1461.7 $[M - H]^{-}$, 1483.6 $[M + Na - 2H]^{-}$.

Linear Lipodepsipeptidyl Resin $C_{11}H_{23}$CO-Glu(O^{t}Bu)-D-Orn(Boc)-D-Tyr(O-Ile-Alloc)-D-Thr(^{t}Bu)-Glu(O^{t}Bu)-D-Val-Pro-Gln(Tr)-Tyr-(Wang)-OAll. Starting from $C_{11}H_{23}$CO-Glu(O^{t}Bu)-D-Orn(Boc)-D-Tyr-D-Thr(^{t}Bu)-Glu(O^{t}Bu)-D-Val-Pro-Gln(Tr)-Tyr(Wang)-OAll, this depsipeptidyl resin was prepared according to the general procedure described above. Acidolytic cleavage of an aliquot of the resulting resin afforded $C_{11}H_{23}$CO-Glu-D-Orn-D-Tyr(O-Ile-Alloc)-D-Thr-Glu-D-Val-Pro-Gln-Tyr-OAll in 82% purity. HPLC (λ = 220 nm) t_R = 9.07 min. MS (ESI) $m/z(+)$: 1562.0 $[M + H]^{+}$, 1583.9 $[M + Na]^{+}$. MS (ESI) $m/z(-)$: 1559.9 $[M - H]^{-}$, 1581.8 $[M + Na - 2H]^{-}$.

Linear Lipodepsipeptidyl Resin $C_{15}H_{31}$CO-Glu(O^{t}Bu)-D-Orn(Boc)-D-Tyr(O-Ile-Alloc)-D-Thr(^{t}Bu)-Glu(O^{t}Bu)-D-Val-Pro-Gln(Tr)-Tyr-(Wang)-OAll. Starting from $C_{15}H_{31}$CO-Glu(O^{t}Bu)-D-Orn(Boc)-D-Tyr-D-Thr(^{t}Bu)-Glu(O^{t}Bu)-D-Val-Pro-Gln(Tr)-Tyr(Wang)-OAll, this depsipeptidyl resin was prepared according to the general procedure described above. Acidolytic cleavage of an aliquot of the resulting resin afforded $C_{15}H_{31}$CO-Glu-D-Orn-D-Tyr(O-Ile-Alloc)-D-Thr-Glu-D-Val-Pro-Gln-Tyr-OAll in 69% purity. HPLC (λ = 220 nm) t_R = 10.13 min. MS (ESI) $m/z(+)$: 1618.0 $[M + H]^{+}$, 1639.9 $[M + Na]^{+}$. MS (ESI) $m/z(-)$: 1616.9 $[M - H]^{-}$, 1638.8 $[M + Na - 2H]^{-}$.

General Method for Allyl/Alloc Removal. Each peptidyl resin was treated with $Pd(PPh_3)_3$ (0.1 equiv) and $PhSiH_3$ (10 equiv) in CH_2Cl_2 under nitrogen for 4 h. After this time, the resulting resin was washed with THF (3 × 15 s), CH_2Cl_2 (3 × 2 min), DMF (10 × 1 min), and CH_2Cl_2 (3 × 2 min) and air dried. An aliquot of each resulting peptidyl resin was exposed to acidolytic conditions of TFA/H_2O/TIS (95:2.5:2.5) for 2 h at room temperature. Following TFA evaporation and diethyl ether extraction, the crude peptide was dissolved in H_2O/CH_3CN, lyophilized, analyzed by HPLC, and characterized by mass spectrometry.

Linear Depsipeptidyl Resin pNZ-Tyr(O-Ile-H)-D-Thr(^{t}Bu)-Glu-(O^{t}Bu)-D-Val-Pro-Gln(Tr)-D-Tyr(Wang)-OH. This peptidyl resin was obtained from **2** following the above general procedure. Acidolytic cleavage of an aliquot of this resin afforded *p*NZ-Tyr(O-Ile-H)-D-Thr-Glu-D-Val-Pro-Gln-D-Tyr-OH in 72% purity. HPLC (λ = 220 nm) t_R = 6.77 min. MS (ESI) $m/z(+)$: 615.2 $[M + H + K]^{2+}$, 1191.5 $[M + H]^{+}$, 1213.5 $[M + Na]^{+}$, 1229.5 $[M + K]^{+}$.

*Linear Lipodepsipeptidyl Resin C_7H_{15}CO-Glu(O^{t}Bu)-D-Orn(Boc)-Tyr(O-Ile-H)-D-Thr(^{t}Bu)-Glu(O^{t}Bu)-D-Val-Pro-Gln(Tr)-D-Tyr(Wang)-OH (**8a**).* This peptidyl resin was obtained from **7a** following the above general procedure. Acidolytic cleavage of an aliquot of **8a** afforded C_7H_{15}CO-Glu-D-Orn-Tyr(O-Ile-H)-D-Thr-Glu-D-Val-Pro-Gln-D-Tyr-OH (**BPC837**) in 76% purity. HPLC (λ = 220 nm) t_R = 6.68 min. MS (ESI) $m/z(+)$: 691.3 $[M + 2H]^{2+}$, 1381.6 $[M + H]^{+}$. MS (ESI) $m/z(-)$: 1379.6 $[M - H]^{-}$, 1401.6 $[M + Na - 2H]^{-}$

Linear Lipodepsipeptidyl Resin C_7H_{15}CO-Glu(O^{t}Bu)-D-Orn(Boc)-Tyr(O-Ile-H)-D-Ser(^{t}Bu)-Glu(O^{t}Bu)-D-Val-Pro-Gln(Tr)-D-Tyr(Wang)-OH. This peptidyl resin was obtained from C_7H_{15}CO-Glu(O^{t}Bu)-D-Orn(Boc)-Tyr(O-Ile-Alloc)-D-Ser(^{t}Bu)-Glu(O^{t}Bu)-D-Val-Pro-Gln-(Tr)-D-Tyr(Wang)-OAll following the above general procedure. Acidolytic cleavage of an aliquot of the resulting resin afforded C_7H_{15}CO-Glu-D-Orn-Tyr(O-Ile-H)-D-Ser-Glu-D-Val-Pro-Gln-D-Tyr-OH (**BPC839**) in 86% purity. HPLC (λ = 220 nm) t_R = 6.65 min. MS (ESI) $m/z(+)$: 684.3 $[M + 2H]^{2+}$, 1367.6 $[M + H]^{+}$. MS (ESI) $m/z(-)$: 1365.6 $[M - H]^{-}$, 1387.6 $[M + Na - 2H]^{-}$.

Linear Lipodepsipeptidyl Resin C_7H_{15}CO-Glu(O^{t}Bu)-D-Orn(Boc)-Tyr(O-Ile-H)-D-Thr(^{t}Bu)-Glu(O^{t}Bu)-D-Ala-Pro-Gln(Tr)-D-Tyr(Wang)-OH. This peptidyl resin was obtained from C_7H_{15}CO-Glu(O^{t}Bu)-D-Orn(Boc)-Tyr(O-Ile-Alloc)-D-Thr(^{t}Bu)-Glu(O^{t}Bu)-D-Ala-Pro-Gln-(Tr)-D-Tyr(Wang)-OAll following the above general procedure. Acidolytic cleavage of an aliquot of the resulting resin afforded C_7H_{15}CO-Glu-D-Orn-Tyr(O-Ile-H)-D-Thr-Glu-D-Ala-Pro-Gln-D-Tyr-OH (**BPC841**) in 82% purity. HPLC (λ = 220 nm) t_R = 6.59 min. MS (ESI) $m/z(+)$: 677.3 $[M + 2H]^{2+}$, 1353.6 $[M + H]^{+}$. MS (ESI) $m/z(-)$: 1351.6 $[M - H]^{-}$, 1373.5 $[M + Na - 2H]^{-}$.

Linear Lipodepsipeptidyl Resin C_7H_{15}CO-Glu(O^{t}Bu)-D-Orn(Boc)-Tyr(O-Ile-H)-D-Ser(^{t}Bu)-Glu(O^{t}Bu)-D-Ala-Pro-Gln(Tr)-D-Tyr(Wang)-OH. This peptidyl resin was obtained from C_7H_{15}CO-Glu(O^{t}Bu)-D-Orn(Boc)-Tyr(O-Ile-Alloc)-D-Ser(^{t}Bu)-Glu(O^{t}Bu)-D-Ala-Pro-Gln-(Tr)-D-Tyr(Wang)-OAll following the above general procedure. Acidolytic cleavage of an aliquot of the resulting resin afforded C_7H_{15}CO-Glu-D-Orn-Tyr(O-Ile-H)-D-Ser-Glu-D-Ala-Pro-Gln-D-Tyr-OH (**BPC843**) in 69% purity. HPLC (λ = 220 nm) t_R = 6.55 min. MS (ESI) $m/z(+)$: 670.3 $[M + 2H]^{2+}$, 1339.6 $[M + H]^{+}$. MS (ESI) $m/z(-)$: 1337.6 $[M - H]^{-}$, 1359.6 $[M + Na - 2H]^{-}$.

Linear Lipodepsipeptidyl Resin C_7H_{15}CO-Glu(O^{t}Bu)-D-Orn(Boc)-D-Tyr(O-Ile-H)-D-Thr(^{t}Bu)-Glu(O^{t}Bu)-D-Val-Pro-Gln(Tr)-Tyr(Wang)-OH. This peptidyl resin was obtained from C_7H_{15}CO-Glu(O^{t}Bu)-D-Orn(Boc)-D-Tyr(O-Ile-Alloc)-D-Thr(^{t}Bu)-Glu(O^{t}Bu)-D-Val-Pro-Gln-(Tr)-Tyr(Wang)-OAll following the above general procedure. Acidolytic cleavage of an aliquot of the resulting resin afforded C_7H_{15}CO-Glu-D-Orn-D-Tyr(O-Ile-H)-D-Thr-Glu-D-Val-Pro-Gln-Tyr-OH (**BPC845**) in 87% purity. HPLC (λ = 220 nm) t_R = 6.82 min. MS (ESI) $m/z(+)$: 1268.6 $[M - Ile + H]^{+}$, 1381.7 $[M + H]^{+}$. MS (ESI) $m/z(-)$: 1266.6 $[M - Ile - H]^{-}$, 1379.6 $[M - H]^{-}$, 1401.6 $[M + Na - 2H]^{-}$.

Linear Lipodepsipeptidyl Resin C_7H_{15}CO-Glu(O^{t}Bu)-D-Orn(Boc)-D-Tyr(O-Ile-H)-D-Ser(^{t}Bu)-Glu(O^{t}Bu)-D-Val-Pro-Gln(Tr)-Tyr(Wang)-OH. This peptidyl resin was obtained from C_7H_{15}CO-Glu(O^{t}Bu)-D-Orn(Boc)-D-Tyr(O-Ile-Alloc)-D-Ser(^{t}Bu)-Glu(O^{t}Bu)-D-Val-Pro-Gln-(Tr)-Tyr(Wang)-OAll following the above general procedure. Acidolytic cleavage of an aliquot of the resulting resin afforded C_7H_{15}CO-Glu-D-Orn-D-Tyr(O-Ile-H)-D-Ser-Glu-D-Val-Pro-Gln-Tyr-OH (**BPC847**) in 93% purity. HPLC (λ = 220 nm) t_R = 6.78 min. MS (ESI) $m/z(+)$: 1254.6 $[M - Ile + H]^{+}$, 1367.7 $[M + H]^{+}$. MS

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(ESI) m/z(−): 1252.5 [M − Ile − H]$^-$, 1365.6 [M − H]$^-$, 1387.6 [M + Na − 2H]$^-$.

Linear Lipodepsipeptidyl Resin C_7H_{15}CO-Glu(O^{t}Bu)-D-Orn(Boc)-D-Tyr(O-Ile-H)-D-Thr(^{t}Bu)-Glu(O^{t}Bu)-D-Ala-Pro-Gln(Tr)-Tyr(Wang)-OH. This peptidyl resin was obtained from C_7H_{15}CO-Glu(O^{t}Bu)-D-Orn(Boc)-D-Tyr(O-Ile-Alloc)-D-Thr(^{t}Bu)-Glu(O^{t}Bu)-D-Ala-Pro-Gln-(Tr)-Tyr(Wang)-OAll following the above general procedure. Acidolytic cleavage of an aliquot of the resulting resin afforded C_7H_{15}CO-Glu-D-Orn-D-Tyr(O-Ile-H)-D-Thr-Glu-D-Ala-Pro-Gln-Tyr-OH (**BPC849**) in 79% purity. HPLC (λ = 220 nm) t_R = 6.73 min. MS (ESI) m/z(+): 677.4 [M + 2H]$^{2+}$, 1240.6 [M − Ile + H]$^+$, 1353.7 [M + H]$^+$. MS (ESI) m/z(−): 1238.5 [M − Ile − H]$^-$, 1351.6 [M − H]$^-$, 1373.6 [M + Na − 2H]$^-$.

Linear Lipodepsipeptidyl Resin C_7H_{15}CO-Glu(O^{t}Bu)-D-Orn(Boc)-D-Tyr(O-Ile-H)-D-Ser(^{t}Bu)-Glu(O^{t}Bu)-D-Ala-Pro-Gln(Tr)-Tyr(Wang)-OH. This peptidyl resin was obtained from C_7H_{15}CO-Glu(O^{t}Bu)-D-Orn(Boc)-D-Tyr(O-Ile-Alloc)-D-Ser(^{t}Bu)-Glu(O^{t}Bu)-D-Ala-Pro-Gln-(Tr)-Tyr(Wang)-OAll following the above general procedure. Acidolytic cleavage of an aliquot of the resulting resin afforded C_7H_{15}CO-Glu-D-Orn-D-Tyr(O-Ile-H)-D-Ser-Glu-D-Ala-Pro-Gln-Tyr-OH (**BPC851**) in 78% purity. HPLC (λ = 220 nm) t_R = 6.67 min. MS (ESI) m/z(+): 1226.6 [M − Ile + H]$^+$, 1339.7 [M + H]$^+$, 1361.6 [M + Na]$^+$. MS (ESI) m/z(−): 1224.5 [M − Ile − H]$^-$, 1337.6 [M − H]$^-$, 1359.6 [M + Na − 2H]$^-$.

*Linear Lipodepsipeptidyl Resin $C_{11}H_{23}$CO-Glu(O^{t}Bu)-D-Orn(Boc)-Tyr(O-Ile-H)-D-Thr(^{t}Bu)-Glu(O^{t}Bu)-D-Val-Pro-Gln(Tr)-D-Tyr(Wang)-OH (**8b**).* This peptidyl resin was obtained from **7b** following the above general procedure. Acidolytic cleavage of an aliquot of **8b** afforded $C_{11}H_{23}$CO-Glu-D-Orn-Tyr(O-Ile-H)-D-Thr-Glu-D-Val-Pro-Gln-D-Tyr-OH (**BPC853**) in 86% purity. HPLC (λ = 220 nm) t_R = 7.45 min. MS (ESI) m/z(+): 719.4 [M + 2H]$^{2+}$, 1437.7 [M + H]$^+$. MS (ESI) m/z(−): 1436.6 [M − H]$^-$, 1457.6 [M + Na − 2H]$^-$

*Linear Lipodepsipeptidyl Resin $C_{15}H_{31}$CO-Glu(O^{t}Bu)-D-Orn(Boc)-Tyr(O-Ile-H)-D-Thr(^{t}Bu)-Glu(O^{t}Bu)-D-Val-Pro-Gln(Tr)-D-Tyr(Wang)-OH (**8c**).* This peptidyl resin was obtained from **7c** following the above general procedure. Acidolytic cleavage of an aliquot of **8c** afforded $C_{15}H_{31}$CO-Glu-D-Orn-Tyr(O-Ile-H)-D-Thr-Glu-D-Val-Pro-Gln-D-Tyr-OH (**BPC855**) in 89% purity. HPLC (λ = 220 nm) t_R = 8.23 min. MS (ESI) m/z(+): 747.4 [M + 2H]$^{2+}$, 1493.8 [M + H]$^+$. MS (ESI) m/z(−): 1491.7 [M − H]$^-$, 1513.7 [M + Na − 2H]$^-$

Linear Lipodepsipeptidyl Resin $C_{11}H_{23}$CO-Glu(O^{t}Bu)-D-Orn(Boc)-D-Tyr(O-Ile-H)-D-Thr(^{t}Bu)-Glu(O^{t}Bu)-D-Val-Pro-Gln(Tr)-Tyr(Wang)-OH. This peptidyl resin was obtained from $C_{11}H_{23}$CO-Glu(O^{t}Bu)-D-Orn(Boc)-D-Tyr(O-Ile-Alloc)-D-Thr(^{t}Bu)-Glu(O^{t}Bu)-D-Val-Pro-Gln-(Tr)-Tyr(Wang)-OAll following the above general procedure. Acidolytic cleavage of an aliquot of the resulting resin afforded $C_{11}H_{23}$CO-Glu-D-Orn-D-Tyr(O-Ile-H)-D-Thr-Glu-D-Val-Pro-Gln-Tyr-OH (**BPC857**) in 62% purity. HPLC (λ = 220 nm) t_R = 7.84 min. MS (ESI) m/z(+): 719.4 [M + 2H]$^{2+}$, 1325.8 [M − Ile + H]$^+$, 1437.9 [M + H]$^+$, 1459.9 [M + Na]$^+$. MS (ESI) m/z(−): 1322.7 [M − Ile − H]$^-$, 1435.8 [M − H]$^-$, 1457.8 [M + Na − 2H]$^-$.

Linear Lipodepsipeptidyl Resin $C_{15}H_{31}$CO-Glu(O^{t}Bu)-D-Orn(Boc)-D-Tyr(O-Ile-H)-D-Thr(^{t}Bu)-Glu(O^{t}Bu)-D-Val-Pro-Gln(Tr)-Tyr(Wang)-OH. This peptidyl resin was obtained from $C_{15}H_{31}$CO-Glu(O^{t}Bu)-D-Orn(Boc)-D-Tyr(O-Ile-Alloc)-D-Thr(^{t}Bu)-Glu(O^{t}Bu)-D-Val-Pro-Gln-(Tr)-Tyr(Wang)-OAll following the above general procedure. Acidolytic cleavage of an aliquot of the resulting resin afforded $C_{15}H_{31}$CO-Glu-D-Orn-D-Tyr(O-Ile-H)-D-Thr-Glu-D-Val-Pro-Gln-Tyr-OH (**BPC859**) in 64% purity. HPLC (λ = 220 nm) t_R = 8.69 min. MS (ESI) m/z(+): 747.5 [M + 2H]$^{2+}$, 758.4 [M + Na + H]$^{2+}$, 1380.9 [M − Ile + H]$^+$, 1494.0 [M + H]$^+$, 1516.9 [M + Na]$^+$. MS (ESI) m/z(−): 1378.8 [M − Ile + H]$^-$, 1491.9 [M − H]$^-$, 1513.9 [M + Na − 2H]$^-$.

Synthesis of the Cyclic Lipodepsipeptides. On-resin cyclization of each linear peptidyl resin was mediated by Oxyma (5 equiv), [ethyl cyano(hydroxyimino)acetato-O^2-tri-(1-pyrrolidinyl)-phosphonium hexafluorophosphate (PyOxim) (5 equiv), and DIEA (10 equiv) in DMF. The reaction mixture was stirred at room temperature for 24 h. The resin was then washed with DMF (6 × 1 min), CH_2Cl_2 (3 × 1 min), and diethyl ether (3 × 2 min) and dried in vacuo. The completion of the cyclization was checked with the Kaiser test.[45] The resulting peptide was cleaved from the resin with TFA/H_2O/TIS (95:2.5:2.5) for 2 h at room temperature. Following TFA evaporation and diethyl ether extraction, the crude peptide was dissolved in H_2O/CH_3CN, lyophilized, and analyzed by HPLC and mass spectrometry.

*Cyclic Depsipeptide pNZ-Tyr(&)-D-Thr-Glu-D-Val-Pro-Gln-D-Tyr-Ile-& (**4**).* Starting from pNZ-Tyr(O-Ile-H)-D-Thr(^{t}Bu)-Glu(O^{t}Bu)-D-Val-Pro-Gln(Tr)-D-Tyr(Wang)-OH, on-resin cyclization followed by acidolytic cleavage afforded the cyclic depsipeptide pNZ-Tyr(&)-D-Thr-Glu-D-Val-Pro-Gln-D-Tyr-Ile-& (**4**) in 31% purity. HPLC (λ = 220 nm) t_R = 7.55 min. MS (ESI) m/z(+): 1195.5 [M + Na]$^+$, 1211.4 [M + K]$^+$. MS (ESI) m/z(−): 1171.5 [M − H]$^-$.

*Cyclic Lipodepsipeptide C_7H_{15}CO-Glu-D-Orn-Tyr(&)-D-Thr-Glu-D-Val-Pro-Gln-D-Tyr-Ile-& (**BPC838**).* Starting from **8a**, on-resin cyclization followed by acidolytic cleavage afforded the cyclic lipodepsipeptide **BPC838** in 33% purity. HPLC (λ = 220 nm) t_R = 7.26 min. MS (ESI) m/z(+): 1363.6 [M + H]$^+$. MS (ESI) m/z(−): 1361.6 [M − H]$^-$. The crude peptide was purified by RP-HPLC obtaining **BPC838** in >99% purity. HPLC (λ = 220 nm) t_R = 7.45 min. ^{1}H NMR (400 MHz, DMSO-d_6 + D_2O) δ (ppm): 0.72−0.87 (m, 18 H), 1.15−1.20 (m, 14 H), 1.41−1.45 (m, 4 H), 1.55−1.60 (m, 3 H), 1.69−1.76 (m, 4 H), 1.82−1.98 (m, 4 H), 2.06−2.26 (m, 10 H), 2.67−2.77 (m, 3 H), 2.86−2.88 (m, 2 H), 3.16−3.27 (m, 2 H), 3.50−3.53 (m, 1 H), 3.97−4.00 (m, 1 H), 4.17−4.26 (m, 3 H), 4.31−4.39 (m, 1 H), 4.44−4.47 (m, 1 H), 4.55−4.63 (m, 2 H), 6.63 (d, 2 H, J = 8.0 Hz), 6.84 (d, 2 H, J = 8.0 Hz), 6.99−7.04 (m, 4 H). MS (ESI) m/z(+): 682.3 [M + 2H]$^{2+}$, 693.3 [M + Na + H]$^{2+}$, 1363.8 [M + H]$^+$, 1385.8 [M + Na]$^+$. MS (ESI) m/z(−): 1361.8 [M − H]$^-$, 1383.6 [M + Na − 2H]$^-$. HRMS (ESI) m/z(+): calcd for $C_{66}H_{99}N_{12}O_{19}$ 1363.7144, found 1363.7130; calcd for $C_{66}H_{98}N_{12}NaO_{19}$ 1385.6963, found 1385.6934; calcd for $C_{66}H_{99}N_{12}NaO_{19}$ 693.3518, found 693.3505; calcd for $C_{66}H_{98}N_{12}Na_2O_{19}$ 704.3428, found 704.3408.

*Cyclic Lipodepsipeptide C_7H_{15}CO-Glu-D-Orn-Tyr(&)-D-Ser-Glu-D-Val-Pro-Gln-D-Tyr-Ile-& (**BPC840**).* Starting from C_7H_{15}CO-Glu-(O^{t}Bu)-D-Orn(Boc)-Tyr(O-Ile-H)-D-Ser(^{t}Bu)-Glu(O^{t}Bu)-D-Val-Pro-Gln(Tr)-D-Tyr(Wang)-OH, on-resin cyclization followed by acidolytic cleavage afforded the cyclic lipodepsipeptide **BPC840** in 35% purity. HPLC (λ = 220 nm) t_R = 7.25 min. MS (ESI) m/z(+): 1349.6 [M + H]$^+$. MS (ESI) m/z(−): 1347.6 [M − H]$^-$. The crude peptide was purified by RP-HPLC obtaining **BPC840** in >99% purity. HPLC (λ = 220 nm) t_R = 7.22 min. ^{1}H NMR (400 MHz, DMSO-d_6 + D_2O) δ (ppm): 0.73−0.86 (m, 15 H), 1.14−1.21 (m, 12 H), 1.41−1.48 (m, 4 H), 1.55−1.61 (m, 3 H), 1.68−1.90 (m, 10 H), 2.00−2.33 (m, 8 H), 2.67−2.77 (m, 2 H), 2.85−2.87 (m, 2 H), 3.19−3.33 (m, 4 H), 3.97−3.99 (m, 1 H), 4.12−4.26 (m, 6 H), 4.35−4.46 (m, 2 H), 4.56−4.60 (m, 1 H), 4.64−4.75 (m, 1 H), 6.63 (d, 2 H, J = 8.0 Hz), 6.86 (d, 2 H, J = 8.0 Hz), 6.95−7.04 (m, 4 H). MS (ESI) m/z(+): 675.3 [M + 2H]$^{2+}$, 1349.7 [M + H]$^+$. MS (ESI) m/z(−): 1347.6 [M − H]$^-$. HRMS (ESI) m/z(+): calcd for $C_{65}H_{97}N_{12}O_{19}$ 1349.6987, found 1349.6962; calcd for $C_{65}H_{96}N_{12}NaO_{19}$ 1371.6807, found 1371.6804; calcd for $C_{65}H_{97}N_{12}NaO_{19}$ 686.3440, found 686.3431; calcd for $C_{65}H_{96}N_{12}Na_2O_{19}$ 697.3350, found 697.3342.

*Cyclic Lipodepsipeptide C_7H_{15}CO-Glu-D-Orn-Tyr(&)-D-Thr-Glu-D-Ala-Pro-Gln-D-Tyr-Ile-& (**BPC842**).* Starting from C_7H_{15}CO-Glu-(O^{t}Bu)-D-Orn(Boc)-Tyr(O-Ile-H)-D-Thr(^{t}Bu)-Glu(O^{t}Bu)-D-Ala-Pro-Gln(Tr)-D-Tyr(Wang)-OH, on-resin cyclization followed by acidolytic cleavage afforded the cyclic lipodepsipeptide **BPC842** in 26% purity. HPLC (λ = 220 nm) t_R = 7.13 min. MS (ESI) m/z(+): 1335.6 [M + H]$^+$. MS (ESI) m/z(−): 1333.6 [M − H]$^-$. The crude peptide was purified by RP-HPLC obtaining **BPC842** in >99% purity. HPLC (λ = 220 nm) t_R = 7.26 min. ^{1}H NMR (400 MHz, DMSO-d_6 + D_2O) δ (ppm): 0.71−0.89 (m, 12 H), 1.10−1.22 (m, 15 H), 1.43−1.45 (m, 4 H), 1.57−1.61 (m, 2 H), 1.71−1.89 (m, 8 H), 1.99−2.22 (m, 10 H), 2.69−2.76 (m, 2 H), 2.84−2.95 (m, 2 H), 3.22−3.25 (m, 1 H), 3.50−3.55 (m, 2 H), 3.98−4.01 (m, 2 H), 4.10−4.14 (m, 1 H), 4.18−4.24 (m, 2 H), 4.38−4.42 (m, 1 H), 4.57−4.61 (m, 1 H), 4.62−4.69 (m, 1 H), 4.81−4.90 (m, 1 H), 6.63 (d, 2 H, J = 8.0 Hz), 6.84 (d, 2 H, J = 8.0 Hz), 6.94 (d, 2 H, J = 8.0 Hz), 7.05 (d, 2 H, J = 8.0 Hz). MS (ESI) m/z(+): 668.3 [M + 2H]$^{2+}$, 1335.7 [M + H]$^+$. MS (ESI) m/z(−): 1333.6 [M − H]$^-$. HRMS (ESI) m/z(+): calcd for

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$C_{64}H_{95}N_{12}O_{19}$ 1335.6831, found 1335.6855; calcd for $C_{64}H_{95}N_{12}NaO_{19}$ 679.3362, found 679.3379; calcd for $C_{64}H_{94}N_{12}Na_2O_{19}$ 690.3271, found 690.3301.

*Cyclic Lipodepsipeptide C_7H_{15}CO-Glu-D-Orn-Tyr(&)-D-Ser-Glu-D-Ala-Pro-Gln-D-Tyr-Ile-& (**BPC844**).* Starting from C_7H_{15}CO-Glu-(O^{t}Bu)-D-Orn(Boc)-Tyr(O-Ile-H)-D-Ser(^{t}Bu)-Glu(O^{t}Bu)-D-Ala-Pro-Gln(Tr)-D-Tyr(Wang)-OH, on-resin cyclization followed by acidolytic cleavage afforded the cyclic lipodepsipeptide **BPC844** in 21% purity. HPLC (λ = 220 nm) t_R = 7.13 min. ^{1}H NMR (400 MHz, DMSO-d_6 + D_2O) δ (ppm): 0.73−0.76 (m, 6 H), 0.83−0.85 (m, 3 H), 1.10−1.20 (m, 15 H), 1.40−1.45 (m, 4 H), 1.56−1.62 (m, 3 H), 1.73−1.88 (m, 8 H), 2.07−2.24 (m, 10 H), 2.71−2.74 (m, 2 H), 2.87−2.91 (m, 2 H), 3.19−3.33 (m, 2 H), 3.47−3.53 (m, 2 H), 3.95−3.97 (m, 1 H), 4.11−4.24 (m, 5 H), 4.36−4.40 (m, 1 H), 4.56−4.62 (m, 2 H), 4.86−4.87 (m, 1 H), 6.63 (d, 2 H, J = 8.0 Hz), 6.86 (d, 2 H, J = 8.0 Hz), 6.94 (d, 2 H, J = 8.0 Hz), 7.06 (d, 2 H, J = 8.0 Hz). MS (ESI) $m/z(+)$: 1321.6 [M + H]$^+$. MS (ESI) $m/z(-)$: 1319.6 [M − H]$^-$. The crude peptide was purified by RP-HPLC obtaining **BPC844** in 94% purity. HPLC (λ = 220 nm) t_R = 7.12 min. MS (ESI) $m/z(+)$: 661.8 [M + 2H]$^{2+}$, 1321.7 [M + H]$^+$. HRMS (ESI) $m/z(+)$: calcd for $C_{63}H_{93}N_{12}O_{19}$ 1321.6674, found 1321.6701; calcd for $C_{63}H_{92}N_{12}NaO_{19}$ 1343.6494, found 1343.6521.

*Cyclic Lipodepsipeptide C_7H_{15}CO-Glu-D-Orn-D-Tyr(&)-D-Thr-Glu-D-Val-Pro-Gln-Tyr-Ile-& (**BPC846**).* Starting from the peptidyl resin C_7H_{15}CO-Glu(O^{t}Bu)-D-Orn(Boc)-D-Tyr(O-Ile-H)-D-Thr(^{t}Bu)-Glu-(O^{t}Bu)-D-Val-Pro-Gln(Tr)-Tyr(Wang)-OH, on-resin cyclization followed by acidolytic cleavage afforded a mixture of the cyclic lipodepsipeptide **BPC846** (17% purity, t_R = 7.19 min) and the linear product from the hydrolysis of the macrolactone C_7H_{15}CO-Glu-D-Orn-D-Tyr-D-Thr-Glu-D-Val-Pro-Gln-Tyr-Ile-OH (17% purity, t_R = 7.04 min) [1:1 ratio by MS (ESI)]. MS (ESI) $m/z(+)$: 1363.7 [M + H]$^+$, 1381.7 [M + H_2O + H]$^+$, 1403.7 [M + H_2O + Na]$^+$. MS (ESI) $m/z(-)$: 1361.7 [M − H]$^-$, 1379.6 [M + H_2O − H]$^-$, 1402.6 [M + H_2O + Na − 2H]$^-$. The crude mixture was purified by RP-HPLC obtaining **BPC846** (59% purity, t_R = 7.11 min) together with the linear product from the hydrolysis of the macrolactone (37% purity, t_R = 6.97 min). MS (ESI) $m/z(+)$: 682.3 [M + 2H]$^{2+}$, 691.3 [M + H_2O + 2H]$^{2+}$, 1363.7 [M + H]$^+$, 1381.7 [M + H_2O + H]$^+$. MS (ESI) $m/z(-)$: 1361.6 [M − H]$^-$, 1379.6 [M + H_2O − H]$^-$. HRMS (ESI) $m/z(+)$: calcd for $C_{66}H_{99}N_{12}O_{19}$ 1363.7144, found 1363.7118; calcd for $C_{66}H_{98}N_{12}NaO_{19}$ 1385.6963, found 1385.6984; calcd for $C_{66}H_{101}N_{12}O_{20}$ 1381.7250, found 1381.7242; calcd for $C_{66}H_{100}N_{12}NaO_{20}$ 1403.7069, found 1403.7063.

*Cyclic Lipodepsipeptide C_7H_{15}CO-Glu-D-Orn-D-Tyr(&)-D-Ser-Glu-D-Val-Pro-Gln-Tyr-Ile-& (**BPC848**).* Starting from the peptidyl resin C_7H_{15}CO-Glu(O^{t}Bu)-D-Orn(Boc)-D-Tyr(O-Ile-H)-D-Ser(^{t}Bu)-Glu-(O^{t}Bu)-D-Val-Pro-Gln(Tr)-Tyr(Wang)-OH, on-resin cyclization followed by acidolytic cleavage afforded a mixture of the cyclic lipodepsipeptide **BPC848** (10% purity, t_R = 7.18 min) and the linear product from the hydrolysis of the macrolactone C_7H_{15}CO-Glu-D-Orn-D-Tyr-D-Ser-Glu-D-Val-Pro-Gln-Tyr-Ile-OH (17% purity, t_R = 7.00 min) [3:4 ratio by MS (ESI)]. MS (ESI) $m/z(+)$: 685.4 [M + H_2O + 2H]$^{2+}$, 1350.7 [M + H]$^+$, 1367.7 [M + H_2O + H]$^+$. MS (ESI) $m/z(-)$: 682.2 [M + H_2O-2H]$^{2-}$, 1348.6 [M − H]$^-$, 1366.7 [M + H_2O − H]$^-$, 1387.6 [M + H_2O + Na − 2H]$^-$. The crude mixture was purified by RP-HPLC obtaining **BPC848** (38% purity, t_R = 7.09 min) together with the linear product from the hydrolysis of the macrolactone (62% purity, t_R = 6.93 min). MS (ESI) $m/z(+)$: 675.3 [M + 2H]$^{2+}$, 1349.7 [M + H]$^+$, 1367.7 [M + H_2O + H]$^+$. MS (ESI) $m/z(-)$: 1347.6 [M − H]$^-$, 1365.6 [M + H_2O − H]$^-$. HRMS (ESI) $m/z(+)$: calcd for $C_{65}H_{97}N_{12}O_{19}$ 1349.6987, found 1349.6999; calcd for $C_{65}H_{96}N_{12}NaO_{19}$ 1371.6807, found 1371.6827; calcd for $C_{65}H_{99}N_{12}O_{20}$ 1367.7093, found 1367.7079; calcd for $C_{65}H_{98}N_{12}NaO_{20}$ 1389.6913, found 1389.6902.

*Cyclic Lipodepsipeptide C_7H_{15}CO-Glu-D-Orn-D-Tyr(&)-D-Thr-Glu-D-Ala-Pro-Gln-Tyr-Ile-& (**BPC850**).* Starting from the peptidyl resin C_7H_{15}CO-Glu(O^{t}Bu)-D-Orn(Boc)-D-Tyr(O-Ile-H)-D-Thr(^{t}Bu)-Glu-(O^{t}Bu)-D-Ala-Pro-Gln(Tr)-Tyr(Wang)-OH, on-resin cyclization followed by acidolytic cleavage afforded a mixture of the cyclic lipodepsipeptide **BPC850** (14% purity, t_R = 7.07 min) and the linear product from the hydrolysis of the macrolactone C_7H_{15}CO-Glu-D-Orn-D-Tyr-D-Thr-Glu-D-Ala-Pro-Gln-Tyr-Ile-OH (16% purity, t_R = 6.93 min) [3:4 ratio by MS (ESI)]. MS (ESI) $m/z(+)$: 677.3 [M + H_2O + 2H]$^{2+}$, 1335.7 [M + H]$^+$, 1353.7 [M + H_2O + H]$^+$, 1375.7 [M + H_2O + Na]$^+$. MS (ESI) $m/z(-)$: 675.1 [M + H_2O-2H]$^{2-}$, 1333.6 [M − H]$^-$, 1351.6 [M + H_2O − H]$^-$, 1373.6 [M + H_2O + Na − 2H]$^-$. The crude mixture was purified by RP-HPLC obtaining **BPC850** (48% purity, t_R = 6.96 min) together with the linear product from the hydrolysis of the macrolactone (52% purity, t_R = 6.84 min). MS (ESI) $m/z(+)$: 668.8 [M + 2H]$^{2+}$, 1335.7 [M + H]$^+$, 1353.6 [M + H_2O + H]$^+$. MS (ESI) $m/z(-)$: 1333.6 [M − H]$^-$, 1351.6 [M + H_2O − H]$^-$. HRMS (ESI) $m/z(+)$: calcd for $C_{64}H_{95}N_{12}O_{19}$ 1335.6831, found 1335.6812; calcd for $C_{64}H_{94}N_{12}NaO_{19}$ 1357.6650, found 1357.6648; calcd for $C_{64}H_{97}N_{12}O_{20}$ 1353.6937, found 1353.6909; calcd for $C_{64}H_{96}N_{12}NaO_{20}$ 1375.6756, found 1375.6727.

*Cyclic Lipodepsipeptide C_7H_{15}CO-Glu-D-Orn-D-Tyr(&)-D-Ser-Glu-D-Ala-Pro-Gln-Tyr-Ile-& (**BPC852**).* Starting from the peptidyl resin C_7H_{15}CO-Glu(O^{t}Bu)-D-Orn(Boc)-D-Tyr(O-Ile-H)-D-Ser(^{t}Bu)-Glu-(O^{t}Bu)-D-Ala-Pro-Gln(Tr)-Tyr(Wang)-OH, on-resin cyclization followed by acidolytic cleavage afforded a mixture of the cyclic lipodepsipeptide **BPC852** (11% purity, t_R = 7.06 min) and the linear product from the hydrolysis of the macrolactone C_7H_{15}CO-Glu-D-Orn-D-Tyr-D-Ser-Glu-D-Ala-Pro-Gln-Tyr-Ile-OH (18% purity, t_R = 6.88 min) [1:2 ratio by MS (ESI)]. MS (ESI) $m/z(+)$: 1321.7 [M + H]$^+$, 1339.7 [M + H_2O + H]$^+$. MS (ESI) $m/z(-)$: 1319.6 [M − H]$^-$, 1337.6 [M + H_2O − H]$^-$, 1359.6 [M + H_2O + Na − 2H]$^-$. The crude mixture was purified by RP-HPLC obtaining **BPC852** (81% purity, t_R = 6.95 min) together with the linear product from the hydrolysis of the macrolactone (19% purity, t_R = 6.78 min). MS (ESI) $m/z(+)$: 1321.6 [M + H]$^+$, 1339.6 [M + H_2O + H]$^+$. MS (ESI) $m/z(-)$: 1319.6 [M − H]$^-$, 1337.6 [M + H_2O − H]$^-$. HRMS (ESI) $m/z(+)$: calcd for $C_{63}H_{93}N_{12}O_{19}$ 1321.6674, found 1321.6653; calcd for $C_{63}H_{92}N_{12}NaO_{19}$ 1343.6494, found 1343.6510; calcd for $C_{63}H_{95}N_{12}O_{20}$ 1339.6780, found 1339.6800; calcd for $C_{63}H_{94}N_{12}NaO_{20}$ 1361.6600, found 1361.6581.

*Cyclic Lipodepsipeptide $C_{11}H_{23}$CO-Glu-D-Orn-Tyr(&)-D-Thr-Glu-D-Val-Pro-Gln-D-Tyr-Ile-& (**BPC854**).* Starting from **8b**, on-resin cyclization followed by acidolytic cleavage afforded the cyclic lipodepsipeptide **BPC854** in 49% purity. HPLC (λ = 220 nm) t_R = 8.21 min. MS (ESI) $m/z(+)$: 1420.8 [M + H]$^+$. MS (ESI) $m/z(-)$: 1417.8 [M − H]$^-$. The crude peptide was purified by RP-HPLC obtaining **BPC854** in 92% purity. HPLC (λ = 220 nm) t_R = 7.99 min. ^{1}H NMR (400 MHz, DMSO-d_6 + D_2O) δ (ppm): 0.71−0.85 (m, 18 H), 1.14−1.19 (m, 18 H), 1.40−1.58 (m, 6 H), 1.61−1.74 (m, 4 H), 1.87−2.25 (m, 14 H), 2.65−2.76 (m, 3 H), 2.80−2.85 (m, 2 H), 3.02−3.21 (m, 2 H), 3.26−3.34 (m, 1 H), 3.48−3.50 (m, 1 H), 3.80−3.87 (m, 2 H), 3.96−4.02 (m, 2 H), 4.11−4.25 (m, 4 H), 4.42−4.46 (m, 1 H), 4.56−4.60 (m, 2 H), 6.61 (d, 2 H, J = 8.0 Hz), 6.83 (d, 2 H, J = 8.0 Hz), 6.99−7.03 (m, 4 H). MS (ESI) $m/z(+)$: 1419.8 [M + H]$^+$. MS (ESI) $m/z(-)$: 1417.7 [M − H]$^-$. HRMS (ESI) $m/z(+)$: calcd for $C_{70}H_{107}N_{12}O_{19}$ 1419.7770, found 1419.7763; calcd for $C_{70}H_{106}N_{12}NaO_{19}$ 1441.7589, found 1441.7593.

*Cyclic Lipodepsipeptide $C_{15}H_{31}$CO-Glu-D-Orn-Tyr(&)-D-Thr-Glu-D-Val-Pro-Gln-D-Tyr-Ile-& (**BPC856**).* Starting from **8c**, on-resin cyclization followed by acidolytic cleavage afforded the cyclic lipodepsipeptide **BPC856** in 50% purity. HPLC (λ = 220 nm) t_R = 9.25 min. MS (ESI) $m/z(+)$: 1475.8 [M + H]$^+$, 1497.8 [M + Na]$^+$. MS (ESI) $m/z(-)$: 1473.8 [M − H]$^-$. The crude peptide was purified by RP-HPLC yielding **BPC856** in 92% purity. HPLC (λ = 220 nm) t_R = 9.23 min. ^{1}H NMR (400 MHz, DMSO-d_6 + D_2O) δ (ppm): 0.79−0.89 (m, 18 H), 1.14−1.22 (m, 28 H), 1.40−1.50 (m, 6 H), 1.56−1.63 (m, 2 H), 1.69−1.77 (m, 2 H), 1.84−2.33 (m, 14 H), 2.68−2.73 (m, 4 H), 2.88−2.90 (m, 2 H), 3.26−3.37 (m, 2 H), 3.60−3.63 (m, 1 H), 4.00−4.04 (m, 2 H), 4.11−4.17 (m, 2 H), 4.23−4.28 (m, 2 H), 4.43−4.46 (m, 1 H), 4.48−4.51 (m, 1 H), 4.56−4.60 (m, 1 H), 4.70−4.73 (m, 1 H), 6.63 (d, 2 H, J = 8.0 Hz), 6.83 (d, 2 H, J = 8.0 Hz), 6.93 (d, 2 H, J = 8.0 Hz), 7.04 (d, 2 H, J = 8.0 Hz). MS (ESI) $m/z(+)$: 738.4 [M + 2H]$^{2+}$, 749.9 [M + Na + H]$^{2+}$, 1475.9 [M + H]$^+$, 1497.9 [M + Na]$^+$. MS (ESI) $m/z(-)$: 1473.9 [M − H]$^-$, 1495.8 [M + Na − 2H]$^-$. HRMS (ESI) $m/z(+)$: calcd for $C_{74}H_{115}N_{12}O_{19}$

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1475.8396, found 1475.8376; calcd for $C_{74}H_{114}N_{12}NaO_{19}$ 1497.8215, found 1497.8227.

*Cyclic Lipodepsipeptide $C_{11}H_{23}$CO-Glu-D-Orn-D-Tyr(&)-D-Thr-Glu-D-Val-Pro-Gln-Tyr-Ile-& (**BPC858**).* Starting from the peptidyl resin $C_{11}H_{23}$CO-Glu(O^{t}Bu)-D-Orn(Boc)-D-Tyr(O-Ile-H)-D-Thr(^{t}Bu)-Glu-(O^{t}Bu)-D-Val-Pro-Gln(Tr)-Tyr(Wang)-OH, on-resin cyclization followed by acidolytic cleavage afforded a mixture of the cyclic lipodepsipeptide **BPC858** (16% purity, t_R = 8.39 min) and the linear product from the hydrolysis of the macrolactone $C_{11}H_{23}$CO-Glu-D-Orn-D-Tyr-D-Thr-Glu-D-Val-Pro-Gln-Tyr-Ile-OH (21% purity, t_R = 8.23 min) [2.5:4 ratio by MS (ESI)]. MS (ESI) $m/z(+)$: 1419.9 [M + H]$^+$, 1437.9 [M + H_2O + H]$^+$, 1459.8 [M + H_2O + Na]$^+$. MS (ESI) $m/z(-)$: 1418.8 [M − H]$^-$, 1435.8 [M + H_2O − H]$^-$, 1457.8 [M + H_2O + Na − 2H]$^-$. The mixture was purified by reverse-phase column chromatography. The cyclic lipodepsipeptide **BPC858** was obtained in 78% purity. HPLC (λ = 220 nm) t_R = 8.14 min. MS (ESI) $m/z(+)$: 1419.9 [M + H]$^+$, 1441.9 [M + Na]$^+$. MS (ESI) $m/z(-)$: 1417.8 [M − H]$^-$, 1439.7 [M + Na − 2H]$^-$. $C_{11}H_{23}$CO-Glu-D-Orn-D-Tyr-D-Thr-Glu-D-Val-Pro-Gln-Tyr-Ile-OH was obtained in 91% purity. HPLC (λ = 220 nm) t_R = 7.99 min. MS (ESI) $m/z(+)$: 1437.9 [M + H]$^+$, 1459.8 [M + Na]$^+$. MS (ESI) $m/z(-)$: 1435.8 [M − H]$^-$, 1457.8 [M + Na − 2H]$^-$.

*Cyclic Lipodepsipeptide $C_{15}H_{31}$CO-Glu-D-Orn-D-Tyr(&)-D-Thr-Glu-D-Val-Pro-Gln-Tyr-Ile-& (**BPC860**).* Starting from the peptidyl resin $C_{15}H_{31}$CO-Glu(O^{t}Bu)-D-Orn(Boc)-D-Tyr(O-Ile-H)-D-Thr(^{t}Bu)-Glu-(O^{t}Bu)-D-Val-Pro-Gln(Tr)-Tyr(Wang)-OH, on-resin cyclization followed by acidolytic cleavage afforded a mixture of the cyclic lipodepsipeptide **BPC860** (24% purity, t_R = 9.04 min) and the linear product from the hydrolysis of the macrolactone $C_{15}H_{31}$CO-Glu-D-Orn-D-Tyr-D-Thr-Glu-D-Val-Pro-Gln-Tyr-Ile-OH (25% purity, t_R = 8.88 min) [2:3 ratio by MS (ESI)]. MS (ESI) $m/z(+)$: 1475.8 [M + H]$^+$, 1493.8 [M + H_2O + H]$^+$, 1515.8 [M + H_2O + Na]$^+$. MS (ESI) $m/z(-)$: 1473.7 [M − H]$^-$, 1491.7 [M + H_2O − H]$^-$, 1514.7 [M + Na − 2H]$^-$. The mixture was purified by reverse-phase column chromatography. Cyclic lipodepsipeptide **BPC860** was obtained in 70% purity. HPLC (λ = 220 nm) t_R = 9.06 min. MS (ESI) $m/z(+)$: 1476.0 [M + H]$^+$, 1497.9 [M + Na]$^+$. MS (ESI) $m/z(-)$: 1473.9 [M − H]$^-$, 1495.8 [M + Na − 2H]$^-$. $C_{15}H_{31}$CO-Glu-D-Orn-D-Tyr-D-Thr-Glu-D-Val-Pro-Gln-Tyr-Ile-OH was obtained in 78% purity. HPLC (λ = 220 nm) t_R = 8.89 min. MS (ESI) $m/z(+)$: 1494.0 [M + H]$^+$, 1516.0 [M + Na]$^+$. MS (ESI) $m/z(-)$: 1491.9 [M − H]$^-$, 1513.9 [M + Na − 2H]$^-$.

General Method for the Hydrolysis of Cyclic Depsipeptides. Cyclic depsipeptide **4** and cyclic lipodepsipeptides **BPC846**, **BPC848**, **BPC850**, **BPC852**, **BPC854**, **BPC856**, **BPC858**, and **BPC860** were treated with a solution of $CH_3OH/H_2O/NH_3$ (4:1:1) for 24 h at room temperature.[42] Next, the mixture was evaporated and the crude residue was dissolved in H_2O/CH_3CN, lyophilized, analyzed by HPLC and characterized by mass spectrometry.

pNZ-Tyr-D-Thr-Glu-D-Val-Pro-Gln-D-Tyr-Ile-OH. The hydrolysis of the peptide **4** was performed following the methodology described above. *p*NZ-Tyr-D-Thr-Glu-D-Val-Pro-Gln-D-Tyr-Ile-OH (t_R = 7.34 min, 26% HPLC purity) together with the methyl ester derivative *p*NZ-Tyr-D-Thr-Glu-D-Val-Pro-Gln-D-Tyr-Ile-OMe (t_R = 7.49 min, 20% HPLC purity) were obtained. MS (ESI) $m/z(+)$: 1191.5 [M + H]$^+$, 1205.5 [M(OMe) + H]$^+$, 1213.5 [M + Na]$^+$, 1227.5 [M(OMe) + Na]$^+$. MS (ESI) $m/z(-)$: 1189.5 [M − H]$^-$, 1203.5 [M(OMe) − H]$^-$.

C_7H_{15}CO-Glu-D-Orn-D-Tyr-D-Thr-Glu-D-Val-Pro-Gln-Tyr-Ile-OH. The hydrolysis of the peptide **BPC846** was performed following the methodology described above. C_7H_{15}CO-Glu-D-Orn-D-Tyr-D-Thr-Glu-D-Val-Pro-Gln-Tyr-Ile-OH (t_R = 7.04 min, 30% HPLC purity) together with the methyl ester derivative C_7H_{15}CO-Glu-D-Orn-D-Tyr-D-Thr-Glu-D-Val-Pro-Gln-Tyr-Ile-OMe (t_R = 7.24 min, 30% HPLC purity) were obtained. MS (ESI) $m/z(+)$: 1381.7 [M + H]$^+$, 1395.7 [M(OMe) + H]$^+$. MS (ESI) $m/z(-)$: 1379.6 [M − H]$^-$, 1393.7 [M(OMe) − H]$^-$, 1401.6 [M + Na − 2H]$^-$, 1415.6 [M(OMe) + Na − 2H]$^-$.

C_7H_{15}CO-Glu-D-Orn-D-Tyr-D-Ser-Glu-D-Val-Pro-Gln-Tyr-Ile-OH. The hydrolysis of the peptide **BPC848** was performed following the methodology described above. C_7H_{15}CO-Glu-D-Orn-D-Tyr-D-Ser-Glu-D-Val-Pro-Gln-Tyr-Ile-OH (t_R = 7.00 min, 28% HPLC purity) together with the methyl ester derivative C_7H_{15}CO-Glu-D-Orn-D-Tyr-D-Ser-Glu-D-Val-Pro-Gln-Tyr-Ile-OMe (t_R = 7.20 min, 27% HPLC purity) were obtained. MS (ESI) $m/z(+)$: 1367.7 [M + H]$^+$, 1381.7 [M(OMe) + H]$^+$, 1389.7 [M + Na]$^+$. MS (ESI) $m/z(-)$: 1365.6 [M − H]$^-$, 1379.7 [M(OMe) − H]$^-$, 1387.6 [M + Na − 2H]$^-$.

C_7H_{15}CO-Glu-D-Orn-D-Tyr-D-Thr-Glu-D-Ala-Pro-Gln-Tyr-Ile-OH. The hydrolysis of the peptide **BPC850** was performed following the methodology described above. C_7H_{15}CO-Glu-D-Orn-D-Tyr-D-Thr-Glu-D-Ala-Pro-Gln-Tyr-Ile-OH (t_R = 6.92 min, 35% HPLC purity) together with the methyl ester derivative C_7H_{15}CO-Glu-D-Orn-D-Tyr-D-Thr-Glu-D-Ala-Pro-Gln-Tyr-Ile-OMe (t_R = 7.12 min, 23% HPLC purity) were obtained. MS (ESI) $m/z(+)$: 1353.6 [M + H]$^+$, 1368.6 [M(OMe) + H]$^+$, 1375.7 [M + Na]$^+$. MS (ESI) $m/z(-)$: 1351.6 [M − H]$^-$, 1365.6 [M(OMe) − H]$^-$, 1387.5 [M(OMe) + Na − 2H]$^-$.

C_7H_{15}CO-Glu-D-Orn-D-Tyr-D-Ser-Glu-D-Ala-Pro-Gln-Tyr-Ile-OH. The hydrolysis of the peptide **BPC852** was performed following the methodology described above. C_7H_{15}CO-Glu-D-Orn-D-Tyr-D-Ser-Glu-D-Ala-Pro-Gln-Tyr-Ile-OH (t_R = 6.87 min, 33% HPLC purity) together with the methyl ester derivative C_7H_{15}CO-Glu-D-Orn-D-Tyr-D-Ser-Glu-D-Ala-Pro-Gln-Tyr-Ile-OMe (t_R = 7.07 min, 30% HPLC purity) were obtained. MS (ESI) $m/z(+)$: 1339.7 [M + H]$^+$, 1353.6 [M(OMe) + H]$^+$, 1361.7 [M + Na]$^+$. MS (ESI) $m/z(-)$: 1337.6 [M − H]$^-$, 1351.7 [M(OMe) − H]$^-$, 1359.5 [M + Na − 2H]$^-$, 1373.5 [M(OMe) + Na − 2H]$^-$.

$C_{11}H_{23}$CO-Glu-D-Orn-Tyr-D-Thr-Glu-D-Val-Pro-Gln-D-Tyr-Ile-OH. The hydrolysis of the peptide **BPC854** was performed following the methodology described above. $C_{11}H_{23}$CO-Glu-D-Orn-Tyr-D-Thr-Glu-D-Val-Pro-Gln-D-Tyr-Ile-OH (t_R = 7.99 min, 30% HPLC purity) together with the methyl ester derivative $C_{11}H_{23}$CO-Glu-D-Orn-Tyr-D-Thr-Glu-D-Val-Pro-Gln-D-Tyr-Ile-OMe (t_R = 8.09 min, 16% HPLC purity) were obtained. MS (ESI) $m/z(+)$: 726.4 [M(OMe) + 2H]$^{2+}$, 1437.8 [M + H]$^+$, 1451.8 [M(OMe) + H]$^+$. MS (ESI) $m/z(-)$: 1435.7 [M − H]$^-$, 1449.8 [M(OMe) − H]$^-$, 1472.7 [M(OMe) + Na − 2H]$^-$.

$C_{15}H_{31}$CO-Glu-D-Orn-Tyr-D-Thr-Glu-D-Val-Pro-Gln-D-Tyr-Ile-OH. The hydrolysis of the peptide **BPC856** was performed following the methodology described above. $C_{15}H_{31}$CO-Glu-D-Orn-Tyr-D-Thr-Glu-D-Val-Pro-Gln-D-Tyr-Ile-OH (t_R = 8.96 min, 20% HPLC purity) together with the methyl ester derivative $C_{15}H_{31}$CO-Glu-D-Orn-Tyr-D-Thr-Glu-D-Val-Pro-Gln-D-Tyr-Ile-OMe (t_R = 9.05 min, 19% HPLC purity) were obtained. MS (ESI) $m/z(+)$: 754.9 [M(OMe) + 2H]$^{2+}$, 1493.9 [M + H]$^+$, 1507.9 [M(OMe) + H]$^+$. MS (ESI) $m/z(-)$: 1491.8 [M − H]$^-$, 1505.8 [M(OMe) − H]$^-$, 1527.7 [M(OMe) + Na − 2H]$^-$.

$C_{11}H_{23}$CO-Glu-D-Orn-D-Tyr-D-Thr-Glu-D-Val-Pro-Gln-Tyr-Ile-OH. The hydrolysis of the peptide **BPC858** was performed following the methodology described above. $C_{11}H_{23}$CO-Glu-D-Orn-D-Tyr-D-Thr-Glu-D-Val-Pro-Gln-Tyr-Ile-OH (t_R = 7.92 min, 43% HPLC purity) together with the methyl ester derivative $C_{11}H_{23}$CO-Glu-D-Orn-D-Tyr-D-Thr-Glu-D-Val-Pro-Gln-Tyr-Ile-OMe (t_R = 8.05 min, 13% HPLC purity) were obtained. MS (ESI) $m/z(+)$: 1437.9 [M + H]$^+$, 1451.9 [M(OMe) + H]$^+$, 1459.9 [M + Na]$^+$. MS (ESI) $m/z(-)$: 1435.8 [M − H]$^-$, 1449.8 [M(OMe) − H]$^-$, 1457.7 [M + Na − 2H]$^-$, 1471.7 [M(OMe) + Na − 2H]$^-$.

$C_{15}H_{31}$CO-Glu-D-Orn-D-Tyr-D-Thr-Glu-D-Val-Pro-Gln-Tyr-Ile-OH. The hydrolysis of the peptide **BPC860** was performed following the methodology described above. $C_{15}H_{31}$CO-Glu-D-Orn-D-Tyr-D-Thr-Glu-D-Val-Pro-Gln-Tyr-Ile-OH (t_R = 8.87 min, 38% HPLC purity) together with the methyl ester derivative $C_{15}H_{31}$CO-Glu-D-Orn-D-Tyr-D-Thr-Glu-D-Val-Pro-Gln-Tyr-Ile-OMe (t_R = 8.94 min, 19% HPLC purity) were obtained. MS (ESI) $m/z(+)$: 1493.9 [M + H]$^+$, 1507.9 [M(OMe) + H]$^+$, 1515.8 [M + Na]$^+$. MS (ESI) $m/z(-)$: 1491.9 [M − H]$^-$, 1505.9 [M(OMe) − H]$^-$, 1513.8 [M + Na − 2H]$^-$.

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ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.8b02553.

Spectral data of amino acids; HPLC and ESI-MS of linear peptides, depsipeptides, and lipodepsipeptides; HPLC, ESI-MS, HRMS, and 1D and 2D NMR of cyclic lipodepsipeptides (PDF)

AUTHOR INFORMATION

Corresponding Authors

*E-mail: lidia.feliu@udg.edu.
*E-mail: marta.planas@udg.edu.

ORCID

Lidia Feliu: 0000-0001-9792-6106
Marta Planas: 0000-0003-4988-4970

Notes

The authors declare no competing financial interest.

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