# Ring-Extended Gramicidin S Analogs Containing *cis* δ-Sugar Amino Acid Turn Mimetics with Varying Ring Size

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Dedicated to Prof. *Dieter Seebach* on the occasion of his 75th birthday

This article presents a series of ring-extended gramicidin S derivatives, **9**–**14**, that have four ornithine residues as polar protonated side chains and one modified turn region containing a mono-functionalized *cis*-δ-oxetane, δ-furanoid, or δ-pyranoid sugar amino acid residue. Of the GS analogs evaluated, we identified compound **7**, which contains the mono-benzyloxy *cis*-δ-pyranoid sugar amino acid, as having a better biological profile than the clinically applied topical antibiotic gramicidin S.

**Introduction.** – The cationic antimicrobial peptide gramicidin S (GS; cyclo(Pro-Val-Orn-Leu-D-Phe)$_2$) adopts a rigid cyclic β-hairpin structure in which the two D-Phe-Pro residues form two-residue turns, and the NH and C=O of opposing Val and Leu residues of the strand regions form four H-bonds (*Fig. 1*). The bacterial membrane-disrupting properties of GS is attributed to the amphiphilic nature of the cyclic β-hairpin structure wherein the hydrophobic side chains of the Leu and Val amino acid residues, and the protonated Orn side chains comprise the apolar and polar face of the molecule, respectively (*Fig. 1*) [1]. As GS also disrupts other biomembranes, its clinical application is limited to topical infections, and for this reason many synthetic studies [2] have been conducted aimed to obtain derivatives with improved therapeutic properties. One interesting approach in this respect is extension of the macrocyclic ring *via* the designed incorporation [3] of four additional amino acid residues in order to finetune the hydrophobicity of the cyclic β-hairpin structure [4]. This strategy is exemplified by tetradecameric analogs **1** and **8** (*Fig. 1*). Compound **1** has four cationic charges and six apolar residues in the strand regions. The replacement of one L-Orn residue with the corresponding D-amino acid residue provides compound **8** with a diminished hydrophobicity, remarkably without dramatically changing the overall cyclic β-hairpin structure [5].

Over the years, we have mainly focused on influencing the conformational behavior of GS *via* the replacement of one of the D-Phe-Pro turn regions with conformationally constrained ω-amino acids [6]. In particular, we applied sugar-derived amino acid

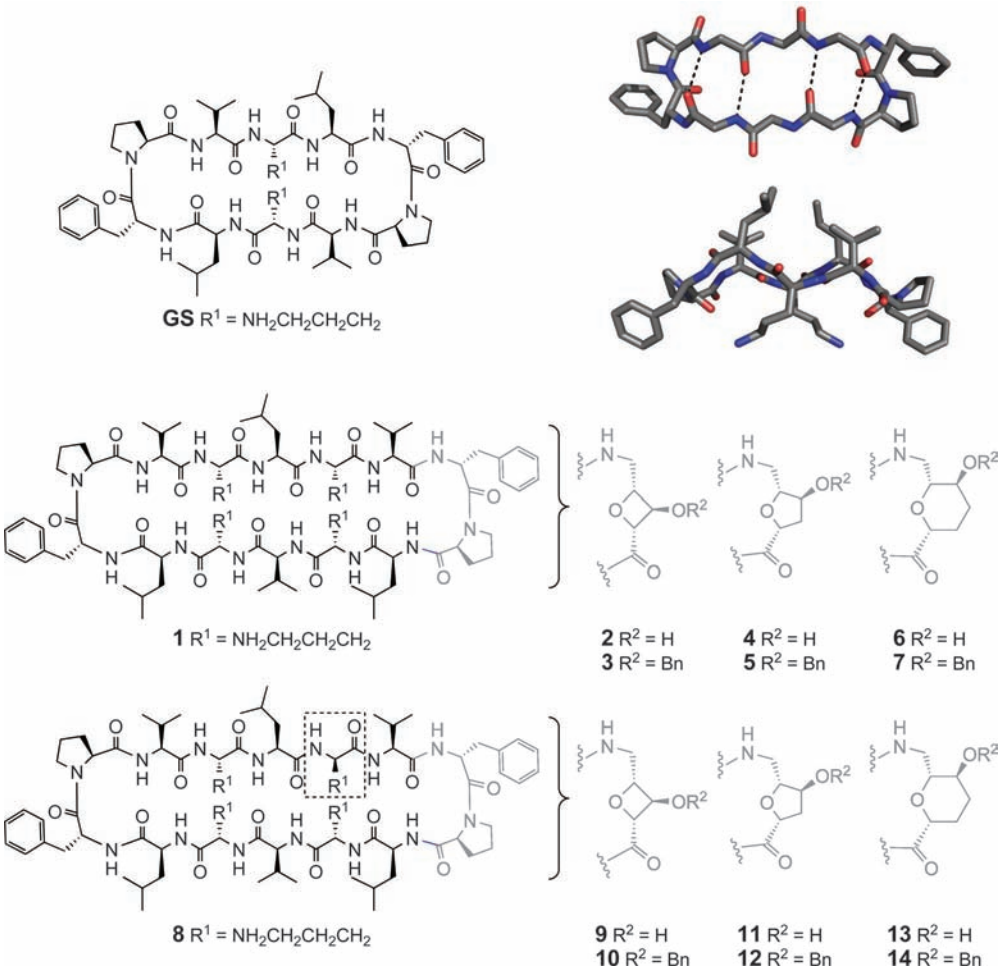


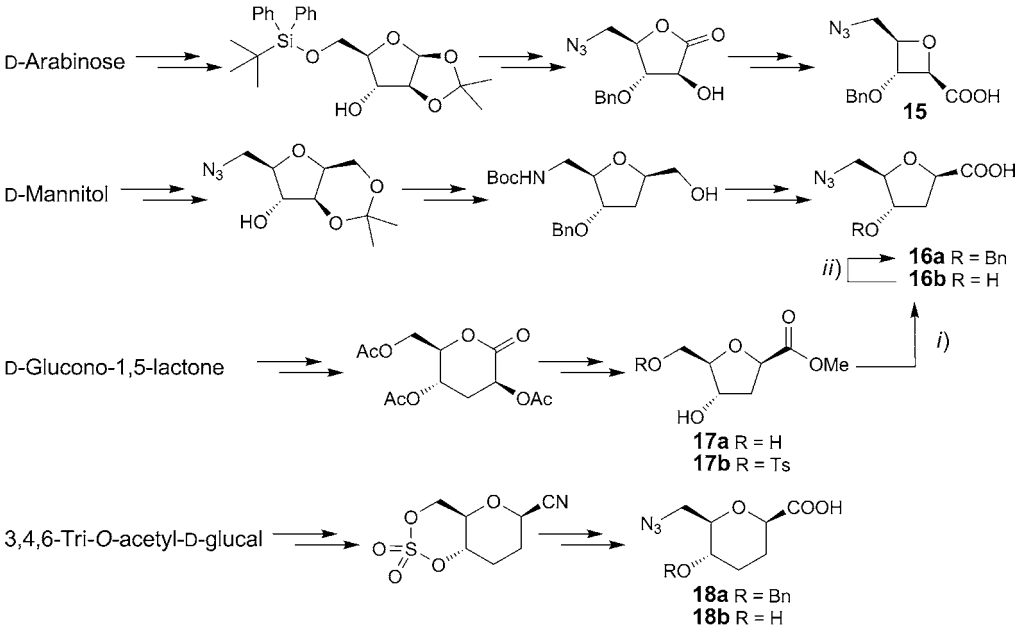

Fig. 1. *The structure of the cyclic decamer antibiotic gramicidin S* (GS)*: top view of its X-ray structure with dashed lines indicating the four intramolecular H-bonds* (side chains omitted for clarity), *and side view showing the hydrophobic face of the molecule formed by the side chains of the Val and Leu residues and the hydrophilic face formed by the two Orn side chains, together with the structures of the tetradecameric GS derivatives* **1** *and* **8**, *and their turn-modified derivatives* **2**–**7** *and* **9**–**14**

building blocks, generally referred to as sugar amino acids (SAAs) [7], as these type of compounds are conformationally biased and can be readily functionalized to obtain a specific substitution pattern on the sugar core. Recently, we reported on the synthesis and biological activity of ring-extended GS derivatives containing *cis* disubstituted furanoid sugar amino acids [5a][8]. The two OH functionalities on the furanoid sugar core in these compounds were used to introduce functionality in order to alter the hydrophobic character of the molecules. As a follow-up of the latter study, we here present the synthesis, conformational analysis, and biological evaluation, using human

erythrocytes and a standard set of bacterial strains, of a series of ring-extended GS derivatives containing mono-functionalized *cis*-*δ*-oxetane, *δ*-furanoid, and *δ*-pyranoid SAA turn mimetics (*i.e.*, compounds **2**–**7** and **9**–**14**, *Fig. 1*).

**Results and Discussion.** – *Syntheses.* The syntheses of the desired *cis*-*δ*-oxetane, *δ*-furanoid-, and *δ*-pyranoid sugar azido acid building blocks **15**, **16a**/**16b**, and **18a**/**b**, generally following previously described procedures, are outlined in *Scheme 1*. The mono-benzyloxy-*cis*-*δ*-oxetane sugar azido acid **15** [6a] is obtained from D-arabinose *via* adaptation of two literature procedures featuring a ring-contraction reaction. *δ*-Furanoid sugar azido acid **16a** is available starting from D-mannitol [6g]. We could shorten the synthetic route towards **16a**/**16b** by converting D-glucono-1,5-lactone to the known [9a] dihydroxy furanoid **17a**, treating the corresponding Ts derivative **17b** with $NaN_3$ in DMF [9b], to obtain **16b**, after saponification of the methyl ester with LiOH in 80% yield, over two steps. Mono-benzylation in the presence of excess NaH provided compound **16a**, albeit in modest yield. Compounds **18a**/**18b** were obtained following our literature procedure [6a] starting from commercially available 3,4,6-tri-*O*-acetyl-D-glucal involving opening of a cyclic sulfate as key step.

Scheme 1. *Overview of the Synthetic Strategy towards δ-Sugar Azido Acids* **15**, **16a/b** *and* **18a/b**

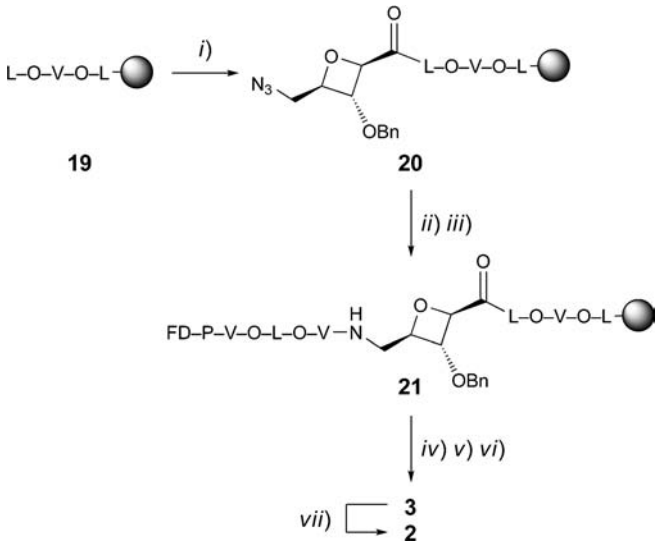



*i*) $NaN_3$, DMF, 85, 0°, 85%. *ii*) Excess NaH, benzyl bromide (BnBr), DMF; 36%.

Peptides **2**–**7** and **9**–**14** were synthesized by using a Fmoc-based peptide coupling protocol, and the corresponding building blocks **15**, **16a**/**16b**, or **18a**/**18b**. The synthetic route is exemplified for the synthesis of peptides **2** and **3** in *Scheme 2*. Thus, acid-labile HMPB-BHA resin was functionalized to obtain pentapeptide **19**. Coupling of sugar azido acid **15** was accomplished with the coupling reagent HCTU in the presence of

$EtN^iPr_2$ to give **20**. After azido reduction on resin using a solution of aqueous $Me_3P$, the peptide sequence was subsequently elongated uneventfully by automated solid-phase chemistry to obtain the full-length immobilized linear sequence **21**. The peptide was released from the resin under mild acidic conditions using 1% TFA and cyclized under high dilute conditions using PyBOP/HOBt. The (*tert*-butoxy)carbonyl (Boc) groups were removed using strong acidic conditions to provide peptide **3** in 20% overall yield after preparative HPLC purification. Peptide **3** was treated with Pd-black under $H_2$ in dioxane in the presence of aqueous HCl to obtain, after preparative HPLC purification, peptide **2** in 80% yield. Similarly, the peptides **5**, **7**, and **9**, **10**, and **12** and **14** were obtained. As the removal of the benzyl (Bn) functionality, upon hydrogenation of the entire peptide, to provide the hydroxylated derivatives, did not proceed well in the case of the furanoid and pyranoid derivatives, building blocks **16b** and **18b** were used to obtain **4**, **11**, and **6**, **13**, respectively.

*Scheme 2*




*i*) Coupling of sugar amino acid (SAA) **15**, 2-(6-chloro-1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethylaminium hexafluorophosphate (HCTU), $EtN^iPr_2$, DMF, 16 h. *ii*) $Me_3P$ (1M in 9:1 THF/$H_2O$, 16 equiv.), 16 h. *iii*) Standard sequential Fmoc solid-phase peptide synthesis (SPPS) (see *Exper. Part* for the details). *iv*) 1% $CF_3COOH$ (TFA) in $CH_2Cl_2$. *v*) (Benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PyBOP), 1-hydroxybenzotriazole (HOBt), $EtN^iPr_2$, DMF. *vi*) TFA/triisopropylsilane (TIS)/$H_2O$ 95:2.5:2.5. *vii*) $H_2$, Pd-black in 1,4-dioxane/aq. HCl.

*NMR Analysis.* The secondary structures of the peptides were analyzed by comparing the coupling constants of the amide H-atoms ($^3J(HN\alpha)$) and chemical-shift perturbations of the $\alpha$-H-atoms ($\Delta\delta H_\alpha$) of peptides **2**–**7** and **9**–**14** with those of peptides **1** and **8** with well-established cyclic $\beta$-hairpin structures in solution [5][10]. These values were extracted from the 600-MHz $^1$H-NMR spectra of the peptides in the solvent $CD_3OD$. The peptide residues were readily assigned using TOCSY and cROESY experiments. Because of the similarity between the non-benzylated and the

benzylated peptides, only the $^3J(NH,H_\alpha)$ and $\Delta\delta(H_\alpha)$ values of the non-benzylated analogs **2**, **4**, **6**, **9**, **11**, and **13**, as well as the peptides **1** and **8** are presented in *Figs. 2* and *3*. The $^3J(NH,H_\alpha)$ values of the Val, Orn, and Leu residues are generally above 7 Hz, which indicates that these residues are part of an extended strand conformation. The D-Phe H-atoms have coupling constants around 3 Hz, which is a typical value for a residue that is part of a turn conformation. This confirms that the peptides adopt cyclic $\beta$-hairpin structures in MeOH. The chemical-shift perturbation of the peptides also corroborated the overall $\beta$-strand character of the Val, Orn, and Leu residues, as these values are above 0.1 ppm. The D-Phe and Pro residues show negative perturbations which is characteristic of a $\beta$-turn region [10].

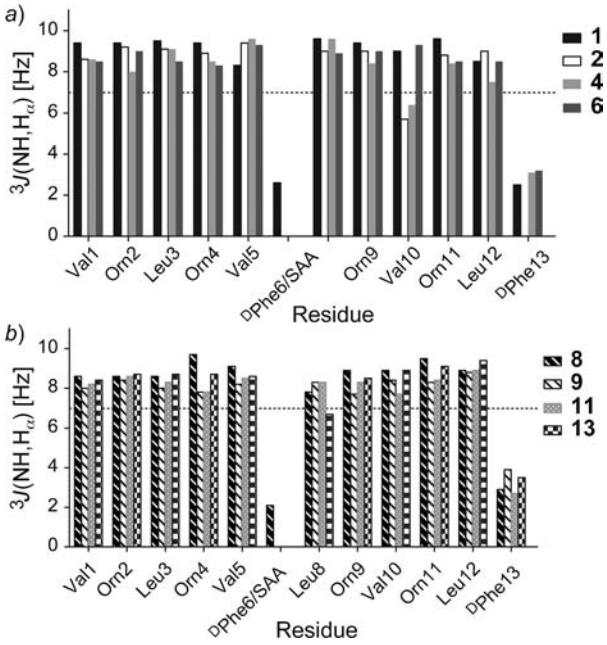



Fig. 2. a) $^3J(NH,H_\alpha)$ *Values of peptides* **1**, **2**, **4**, *and* **6** *containing* L-*ornithines*; b) $^3J(NH,H_\alpha)$ *values of peptides* **8**, **9**, **11**, *and* **13** *having one* D-*ornithine*. Numbering of amino acids N → C: cyclo(Val(1)-Orn(2)-Leu(3)-Orn(4)-Val(5)-SAA-Leu(8)-Orn(9)-Val(10)-Orn(11)-Leu(12)-D-Phe(13)-Pro(14)).

When focusing on the details, it should be noted that the $^3J(NH,H_\alpha)$ values of the Val(10) of the oxetane and furanoid containing peptides are markedly lower than the values obtained with the pyranoid-containing peptides (as is illustrated in *Fig. 2*, *a*, for peptides **2**, **4**, and **6**). This slight deviation of the $^3J(NH,H_\alpha)$ value of one of the strand residues may indicate a partial conformational flexibility and confirm [6a] that the pyranoid sugar amino acid residue is a better replacement of the D-Phe-Pro than the oxetane and furanoid sugar amino acids with respect to maintaining $\beta$-strand integrity.

*Antimicrobial and Hemolytic Activity.* The antimicrobial activity of peptides **1**–**14** and GS was investigated using our standard panel of *Gram*-positive and *Gram*-negative bacteria (*Table*). The toxicity of the peptides was evaluated by performing a hemolytic assay using human erythrocytes (*Table*). The reversed-phase HPLC retention times as

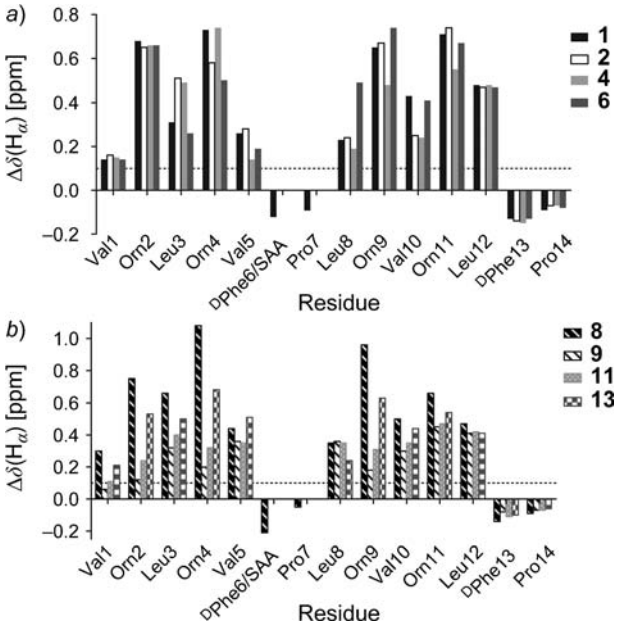



Fig. 3. a) *Δδ(H$_\alpha$) Values of peptides* **1**, **2**, **4**, *and* **6** *having* L-*ornithines*; b) *Δδ(H$_\alpha$) values of the peptides* **8**, **9**, **11**, *and* **13** *having one* D-*ornithine*. $\Delta\delta(H_\alpha) = \delta(H_\alpha) - \delta(H_\alpha)$ random coil. The $\delta(H_\alpha)$ values of the amino acid residues in GS are not significantly affected when using MeOH instead of $H_2O$ as solvent system. For the Orn residues, the random coil value of Lys was used.

a measure of peptide hydrophobicity [11] show that the presence of a D-Orn residue in the sequence provides a more hydrophilic peptide series (*i.e.*, **8**–**14**) than the series with only L-Orn residues (*i.e.*, **1**–**7**; *Table*). Peptides **9**–**14**, generally with low hemolytic activities, only displayed modest antimicrobial activities against the *Gram*-positive strain *S. epidermidis*. In contrast, analogs **2**–**7** display antimicrobial activities against all tested strains.

Notable is the higher activity of **2**–**7** against *Gram*-negative bacteria compared to GS and peptide **1**. Peptides **2**, **5**, and **7** have potent and broad-spectrum antibacterial activities. Peptide **7** has a slightly better hemolytic value than GS.

To give a complete overview, we also included the properties of the known [4] compounds **22** and **26**, as well as the previously reported [5a][8] compounds **23**–**25** and **27**–**29** (*Table* and *Fig. 4*).

**Conclusions.** – A study is presented in which subtle changes in hydrophobicity were introduced in a series of cyclic ring-extended GS analogs by replacement of one of the two-residue turns with sugar amino acid residues varying in ring size and having a hydroxy or benzyloxy functionality combined with a single L/D-ornithine substitution in one of the strands. To this end, peptides **2**–**7** and **9**–**14** were prepared, and their conformational and biological properties were compared with those of GS and the known peptides **1** and **8**. According to NMR, the peptides **2**–**7** and **9**–**14** have similar

Table. *Antimicrobial Activities* (*MICs*) *against a Standard Set of* Gram-*Positive and* Gram-*Negative bacteria, Retention Times, and Hemolytic Activities of GS and of the Peptides* **1**–**14**. Included are also the data of the previously published [5a][8] peptides **22**–**29** (**22** is the reference compound GS14, **26** is the reference compound GS14K4; for structures, see *Fig. 4*).

| Analogs | Retention time[a]) | *S. aureus*[b]) | *S. epidermidis*[b]) | *E. faecalis*[b]) | *B. cereus*[b]) | *P. aeruginosa*[c]) | *E. coli*[c]) | 100% Hemolysis[d]) |
|---|---|---|---|---|---|---|---|---|
| GS | 8.38 | 4 | 2 | 8 | 4 | 64 | 32 | 31.5 |
| **1** | 7.67 | 32 | 2 | 32 | 32 | 64 | 32 | 3.9 |
| **2** | 6.63 | 8 | 1 | 4 | 2 | 4 | 2 | 31.5 |
| **3** | 6.67 | 8 | 2 | 16 | 16 | 16 | 8 | 62.5 |
| **4** | 6.71 | 16 | 8 | 16 | 16 | 16 | 16 | 31.5 |
| **5** | 7.30 | 4 | 4 | 8 | 8 | 8 | 8 | 31.5 |
| **6** | 6.67 | 32 | 8 | 32 | 32 | 32 | 16 | 31.5 |
| **7** | 7.42 | 4 | 2 | 8 | 8 | 8 | 16 | 62.5 |
| **8** | 6.25 | 64 | 4 | 64 | 16 | > 64 | 64 | 62.5 |
| **9** | 5.76 | > 64 | 16 | > 64 | 64 | 64 | 64 | 250 |
| **10** | 6.34 | 32 | 4 | 64 | 16 | 32 | 16 | 125 |
| **11** | 5.79 | > 64 | 16 | > 64 | > 64 | > 64 | 64 | > 500 |
| **12** | 6.31 | 32 | 4 | 64 | 16 | 64 | 16 | 125 |
| **13** | 5.56 | > 64 | 64 | > 64 | > 64 | > 64 | > 64 | > 500 |
| **14** | 6.15 | > 64 | 8 | > 64 | 32 | > 64 | 32 | 500 |
| **22** | 7.26 | > 64 | 64 | 32 | 32 | > 64 | > 64 | 3.9 |
| **23** | 6.23 | 4 | 4 | 8 | 2 | 16 | 16 | 15.6 |
| **24** | 6.28 | 4 | 4 | 8 | 4 | 16 | 16 | 15.6 |
| **25** | 5.70 | 8 | 4 | 8 | 4 | 16 | 8 | 31.3 |
| **26** | 5.95 | 64 | 8 | 64 | 16 | > 64 | 64 | 500 |
| **27** | 5.67 | 8 | 8 | 16 | 8 | 64 | 32 | 500 |
| **28** | 5.33 | 16 | 8 | 32 | 8 | 64 | 32 | 500 |
| **29** | 4.98 | > 64 | 16 | > 64 | 64 | > 64 | 64 | > 500 |

[a]) Retention times from RP-HPLC in min (see *Exper. Part*). [b]) *Gram*-positive bacteria, *MIC* in mg/l. [c]) *Gram*-negative bacteria, *MIC* in mg/l. [d]) Hemolytic activity (100% lysis of the erythrocytes) in μM.

conformational properties as the peptides **1** and **8** in the solvent MeOH, which is in agreement with an overall cyclic $\beta$-hairpin conformation. The peptides **9**–**14** having a D-ornithine substitution are largely biologically inactive. Based on their HPLC retention times under controlled conditions, this finding is in agreement with the general trend that hydrophilic peptides of this type are not antimicrobial [4b][12]. The more hydrophobic peptides **2**–**7** exhibit antimicrobial activities against both *Gram*-positive and *Gram*-negative bacteria. The best compound in this series is peptide **7**, containing the *cis*-mono-benzyloxy-pyranoid sugar amino acid residue, having potent and broad spectrum antibacterial activity within the small set of bacterial strains tested, and a somewhat better hemolytic value than GS. This finding seems to confirm [6a] that the *cis*-mono-benzyloxy-pyranoid sugar amino acid residue is a good, slightly less hydrophobic mimic of the D-Phe-Pro two-residue turn. It should be noted that the differences in hemolytic values are not large indicating that the peptides **2**, **5**, and the previously reported compound **25** also have interesting biological properties.

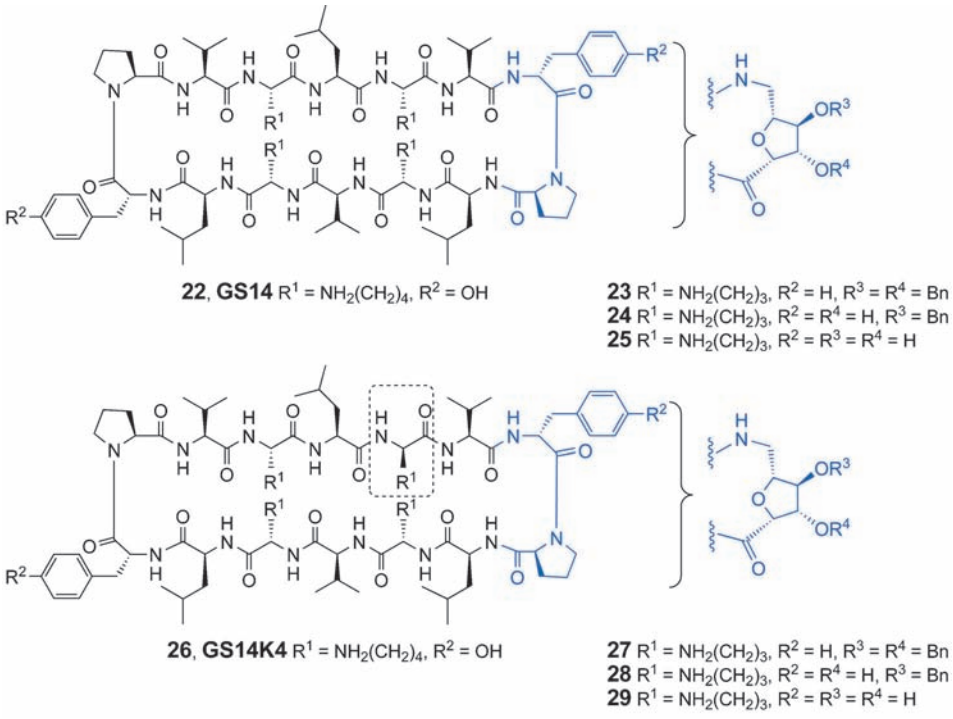



Fig. 4. *Structures of the known tetradecameric gramicidin S derivatives GS14 and GS14K4,* **24** *and* **26**, *respectively, and the previously published analogs with a disubstituted furanoid SAA modified β-turn,* **23**–**25** *and* **27**–**29**

We are grateful to *Kees Erkelens* and *Fons Lefeber* for assistance in recording the NMR spectra. This work was supported by a grant from the Leiden Institute of Chemistry.

## Experimental Part

*General*. Light petroleum ether (PE) with a boiling range of 40–60° was used. All other solvents used under anh. conditions were stored over 4-Å molecular sieves except for MeOH which was stored over 3-Å molecular sieves. Solvents used for workup and silica-gel column chromatography (CC) were of technical grade and distilled before use. All other solvents were used without further purification. Reactions were monitored by TLC. The linear peptides were cleaved from resin, cyclized, and purified by RP-HPLC (*Gilson GX-281*) with a prep. *Gemini C18* column (*Phenomenex*, 5-μm particle size) or semi-prep. (250 × 21.2 mm, 5-μm particle size). The applied eluents were *A:* 0.1 % aq. TFA, *B:* MeCN. The linear peptides and cyclized peptides were analyzed with LC/MS (detection simultaneously at 214 and 254 nm) equipped with an anal. *C18* column (4.6 mm × 250 mm, 5-μm particle size). The applied eluents were *A:* $H_2O$, *B:* MeCN, and *C:* 1.0% aq. TFA. HR-MS: direct injection (2 μl of a 2 μM soln. in $H_2O$/MeCN 50:50 (*v*/*v*) and 0.1% HCOOH) on a mass spectrometer *Thermo Finnigan LTQ Orbitrap* equipped with an electrospray ion source in positive-ion mode (source voltage, 3.5 kV; sheath gas flow, 10; cap. temp., 523 K) with resolution $R = 60000$ at $m/z$ 400 (mass range $m/z$ 150–2000) and dioctyl phthalate ($m/z$ 391.28428) as lock mass. Hemolytic curves were analyzed with Graphpad Prism version 5.01 for Windows, *GraphPad Software*, San Diego California USA. Optical rotations were measured on a

*Propol* automatic polarimeter (sodium D-line, $\lambda$ 589 nm). Specific rotations $[\alpha]_D$ are given in degrees per centimeter and the concentration *c* is given in mg/ml in the specific solvent.

*NMR Spectroscopy.* $^1$H- and $^{13}$C-APT NMR for all intermediates were recorded on a *Bruker AV-400* (400 and 100 MHz, resp.) or a *Bruker DMX 600*. The spectra of the peptides **2**–**7** and **9**–**14** were recorded on a *Bruker DMX 600* equipped with a pulsed-field gradient accessory and a cryo-probe. For the cROESY spectra (200-ms mixing time), the peptides were dissolved in $CD_3OD$. Standard DQF-COSY (512c × 2084c) and TOCSY (400c × 2048c) spectra were recorded using presaturation for solvent suppression. cROESY spectra (400c × 2048c, $\tau_{mix}$ 180 ms) were recorded using the presat solvent suppression. All spectra were recorded in phase-sensitive mode, using either the TPPI or states-TPPI for quadrature detection in the indirect dimension. Homonuclear coupling constants were determined from the corresponding $^1$H spectra.

*Synthesis of Methyl 2,5-Anhydro-3-deoxy*-D-ribo-*hexonate* (**17a**). Following the procedure described in [9a]: D-glucono-1,5-lactone (40 g, 225 mmol) was added in portions during 10–15 min to $Ac_2O$ (100 ml, 1 mol) containing a few drops of 60% aq. $HClO_4$. The mixture was kept for 1 h at r.t., and the clear soln. was subsequently concentrated *in vacuo*. The crude product was dissolved in $CH_2Cl_2$ (300 ml) and cooled to 0°, and $Et_3N$ (48 ml, 1,5 mol) was added in one portion. The yellow soln. was kept for 15 min at 0°, and subsequently washed with 2M HCl and with $H_2O$, dried ($Na_2SO_4$) and concentrated *in vacuo*. The residue was purified by CC (AcOEt/PE 1:3) to give 2,4,6-tri-*O*-acetyl-3-deoxy-D-*erythro*-hex-2-enono-1,5-lactone (=(2*R**,3*S**)-2-[(acetyloxy)methyl]-6-oxo-3,6-dihydro-2*H*-pyran-3,5-diyl diacetate; 65 g, 225 mmol, 100%). Colorless syrup. The spectroscopic data were in agreement with those reported in [9a]. $^1$H-NMR (400 MHz, $CDCl_3$): 6.45 (*d*, *J* = 4.2, H–C(3)); 5.63 (*dd*, *J* = 5.8, 4.2, H–C(4)); 4.77 (*dd*, *J* = 10.3, 4.6, H–C(5)); 4.36 (*ddd*, *J* = 34.8, 12.3, 4.6, $CH_2$(6)); 2.27 (*s*, Ac); 2.14 (*s*, Ac); 2.11 (*s*, Ac). $^{13}$C-NMR (101 MHz, $CDCl_3$): 170.4, 169.7, 168.1 (3 CO); 157.2 (C(1)); 139.6 (C(2)); 126.1 (C(3)); 77.8 (C(5)); 64.2 (C(4)); 62.0 (C(6)); 20.7, 20.6, 20.3 (3 Ac).

2,4,6-Tri-*O*-acetyl-3-deoxy-D-*erythro*-hex-2-enono-1,5-lactone (57.2 g, 200 mmol) was dissolved in AcOEt (200 ml) and hydrogenated for 16 h at 65 bar in the presence of 10% Pd/C. Filtration and concentration gave 2,4,6-tri-*O*-acetyl-3-deoxy-D-*arabino*-hexono-1,5-lactone (=(2*R*,3*S*,5*S*)-2-[(acetyloxy)methyl]-6-oxotetrahydro-2*H*-pyran-3,5-diyl diacetate; 52.7 g, 183 mmol, 92%). Colorless syrup. The spectroscopic data were in agreement with those reported in [9a]. $^1$H-NMR (400 MHz, $CDCl_3$): 5.58 (*dd*, *J* = 12.4, 7.1, H–C(2)); 5.19 (*td*, *J* = 6.1, 3.2, H–C(4)); 4.65–4.60 (*m*, H–C(5)); 4.36 (*dd*, *J* = 12.3, 3.6, H–C(6)); 4.27 (*dd*, *J* = 12.3, 5.0, H–C(6′)); 2.44 (*ddd*, *J* = 14.3, 12.4, 6.2, H–C(3)); 2.38–2.26 (*m*, H–C(3′)); 2.19 (*s*, Ac); 2.14 (*s*, Ac); 2.11 (*s*, Ac). $^{13}$C-NMR (101 MHz, $CDCl_3$): 170.3, 169.7, 167.3 (3 CO); 77.3 (C(5)); 65.7 (C(4)); 64.0 (C(2)); 62.7 (C(6)); 30.5 (C(3)); 20.9, 20.7, 20.6 (3 Ac).

2,4,6-Tri-*O*-acetyl-3-deoxy-D-*arabino*-hexono-1,5-lactone (18.48 g, 64.11 mmol in MeOH (100 ml)) was treated with MeONa (0.02N of 5.56M MeONa in MeOH). The mixture was stirred for 3 h, after which it was acidified with *Dowex* $H^+$ (pH 5). The mixture was heated for 16 h at 50°. The resin was removed by filteration, and the mixture was concentrated *in vacuo*. The crude residue was dissolved in acetone, and $H_2SO_4$ (1 ml) and $MgSO_4$ (10 g) were added. After completion ($R_f$ (AcOEt) 0.6), the mixture was neutralized with $Et_3N$ and filtered over *Celite*®. The mixture was concentrated and subjected to a flash CC (AcOEt/PE 1:1) to yield 3-deoxy-5,6-*O*-isopropylidene-D-*arabino*-hexono-1,4-lactone (=(3*R**,5*R**)-5-(2,2-dimethyl-1,3-dioxolan-4-yl)-3-hydroxydihydrofuran-2(3*H*)-one; 9.816 g, 48.55 mmol, 76%). The spectroscopic data were in agreement with those reported in [9c]. $^1$H-NMR (400 MHz, MeOD): 4.56 (*dd*, *J* = 10.7, 8.7, H–C(2)); 4.44–4.39 (*m*, H–C(4)); 4.26 (*dd*, *J* = 11.9, 5.6, H–C(5)); 4.13 (*dd*, *J* = 8.6, 6.7, H–C(6)); 3.84 (*dd*, *J* = 8.7, 5.4, H–C(6′)); 2.69–2.63 (*m*, H–C(3)); 1.98 (*q*, *J* = 10.4, H–C(3′)); 1.42 (*s*, Me); 1.35 (*s*, Me). $^{13}$C-NMR (101 MHz, MeOD): 178.5 (CO); 111.1 ($Me_2C$=); 77.7 (C(5)); 77.3 (C(4)); 68.8 (C(2)); 66.8 (C(6)); 34.1 (C(3)); 26.6 (Me); 25.2 (Me).

3-Deoxy-5,6-*O*-isopropylidene-D-*arabino*-hexono-1,4-lactone (9.78 g, 48.37 mmol) was co-evaporated with toluene and dissolved in pyridine (50 ml). The mixture was cooled to 0° and MsCl (2 equiv. 7.49 ml) was added dropwise. After 1 h, the reaction was completed ($R_f$ (AcOEt) 0.8). Ice and $H_2O$ were added, keeping the temp. at 0°, which caused the product to precipitate. The solids were removed by filteration, the filtrate washed with $H_2O$ and $Et_2O$, and dried to give 2-*O*-mesyl-3-deoxy-5,6-*O*-isopropylidene-D-*arabino*-hexono-1,4-lactone (=(3*R**,5*R**)-5-(2,2-dimethyl-1,3-dioxolan-4-yl)-2-oxotetrahydrofuran-3-yl methanesulfonate; 7.02 g, 25.03 mmol, 76%). The spectroscopic data were in

agreement with those reported in [9d]. $^1$H-NMR (600 MHz, $CDCl_3$, $T = 303$ K): 5.38 (*t*, *J* = 9.5, H–C(2)); 4.39 (*dt*, *J* = 9.2, 6.3, H–C(4)); 4.21 (*dd*, *J* = 11.2, 6.3, H–C(5)); 4.14 (*dd*, *J* = 8.8, 6.6, H–C(6)); 3.90 (*dd*, *J* = 9.0, 4.6, H–C(6′)); 3.27 (*s*, MeS); 2.90 (*ddd*, *J* = 14.5, 8.9, 5.9, H–C(3)); 2.39 (*dt*, *J* = 13.2, 9.8, H–C(3′)); 1.45 (*s*, Me); 1.36 (*s*, Me).

A suspension of 2-*O*-mesyl-3-deoxy-5,6-*O*-isopropylidene-D-arabino-hexono-1,4-lactone (7.02 g, 25.03 mmol) in $H_2O$ (50 ml) and TFA (0.5 ml) was boiled for 3 h. The soln. was concentrated, and the residue was dissolved in MeOH (100 ml), and *Amberlite IR120 H*$^+$ was added. The soln. was stirred for 3 h. The *Amberlite* was filtered off, and the mixture was neutralized with $Et_3N$ and concentrated. The methyl ester was purified with CC (AcOEt 100%) to yield **17a** (2.46 g, 13.94 mmol 59%). Colorless oil. The spectroscopic data were in agreement with those reported in [9a]. $^1$H-NMR (400 MHz, MeOD): 4.68–4.61 (*m*, H–C(1)); 4.27 (*dt*, *J* = 5.7, 2.8, H–C(3)); 3.91 (*td*, *J* = 5.0, 2.9, H–C(4)); 3.75 (*s*, Me); 3.58–3.56 (*m*, $CH_2$(5)); 2.29–2.09 (*m*, $CH_2$(2)). $^{13}$C-NMR (101 MHz, MeOD): 175.3 (CO); 89.5 (C(4)); 77.3 (C(1)); 73.2 (C(3)); 63.5 (C(5)); 52.9 (Me); 39.7 (C(2)).

*2,5-Anhydro-6-azido-3-deoxy*-D-ribo-*hexonic Acid* (**16b**). Following the procedure in [9b]: compound **17a** (419 mg, 2.38 mmol) was coevaporated with toluene (3 × 50 ml) and dissolved in $CH_2Cl_2$ (100 ml), and $Et_3N$ (1.2 equiv., 397 µl), TsCl (1.1 equiv., 499 mg), and DMAP (= 4-(dimethylamino)pyridine; 10 mg) were added, and the mixture was stirred until completion ($R_f$ (AcOEt/PE 1:1) 0.50). The mixture was washed with 1M HCl, sat. aq. $NaHCO_3$, and brine. The org. layer was dried ($Na_2SO_4$) and concentrated. The residue was subjected to a CC (AcOEt/PE 1:4) to yield **17b** (566 mg, 1.71 mmol, 72%). Slightly yellow oil.

Compound **17b** (1.65 g, 1.55 mmol) was dissolved in DMF (50 ml), and $NaN_3$ was added (5 equiv., 1.62 g). The mixture was heated for 16 h at 85°. DMF was evaporated. The residue was subjected to CC (AcOEt/PE 1:4) and yielded methyl 2,5-anhydro-6-azido-3,6-dideoxy-D-*ribo*-hexonate as a colorless oil (264 mg, 1.33 mmol, 85%). The spectroscopic data were in agreement with those reported in [9b]. $^1$H-NMR (400 MHz, $CDCl_3$): 4.71 (*t*, *J* = 7.7, H–C(2)); 4.35 (*dd*, *J* = 8.1, 4.7, H–C(4)); 4.05 (*td*, *J* = 5.4, 3.2, H–C(5)); 3.77 (*s*, MeO); 3.45 (*qd*, *J* = 12.8, 5.4, $CH_2$(6)); 2.29 (*dd*, *J* = 7.8, 4.8, $CH_2$(3)); 1.86 (br. *s*, OH). $^{13}$C-NMR (101 MHz, $CDCl_3$): 172.31 (CO); 85.7 (C(5)); 76.6 (C(2)); 73.5 (C(4)); 52.6 (C(6)); 52.3 (MeO); 38.7 (C(3)).

2,5-Anhydro-6-azido-3,6-dideoxy-D-*ribo*-hexonate (1.31 mmol) was dissolved in THF/$H_2O$ 7:1 (16 ml) and stirred for 3 h. The solvent was evaporated, and the residue was dissolved in $H_2O$ (50 ml) and excess *Amberlyte H*$^+$. The mixture was stirred for 2 h, and the resin was removed by filtration. The filtrate was evaporated *in vacuo* to yielding **16b** (1.24 mmol, 232 mg, 95%). $R_f$ (AcOEt/PE 1:1, 1% AcOH) 0.1. $[\alpha]_D^{20} = +39.6$ (*c* = 0.5, $^i$PrOH). $^1$H-NMR (400 MHz, $CDCl_3$): 4.73 (*t*, *J* = 7.6, H–C(2)); 4.37 (*dd*, *J* = 9.7, 5.4, H–C(4)); 4.08 (*q*, *J* = 4.3, H–C(5)); 3.61 (*qd*, *J* = 13.0, 4.3, $CH_2$(6)); 2.38 (*dd*, *J* = 7.6, 5.5, $CH_2$(3)). $^{13}$C-NMR (101 MHz, $CDCl_3$): 173.2 (CO); 85.0 (C(4)); 76.2 (C(1)); 72.5 (C(3)); 51.9 (C(5)); 38.8 (C(2)). HR-ESI-MS: 188.0665 ($[M+H]^+$, $C_6H_{10}N_3O_4^+$; calc. 188.0666).

*2,5-Anhydro-6-azido-4-*O*-benzyl-3,6-dideoxy*-D-ribo-*hexonic Acid* (**16a**). Compound **16b** (133 mg, 0.71 mmol) was dissolved in DMF and cooled to 0°, and NaH was added (2.5 equiv., 71 mg). Subsequently, BnBr was added (1.1 equiv., 92 µl). The soln. was stirred for 3 h at 0°, and product formation was observed by TLC ($R_f$ (AcOEt, 1% AcOH) 0.57). The reaction was quenched with $H_2O$, and the volatiles were evaporated. The mixture was stirred with *DOWEX H*$^+$ for 1 h in $H_2O$. The resin was removed by filtration, and the solvent was evaporated. The crude product was subjected to CC (AcOEt/PE 1:4, 1% AcOH) and the product was collected as a colorless oil (71 mg, 0.25 mmol, 36%). *Note:* this reaction is prone for epimerization, and keeping the soln. at 0° is essential. The spectroscopic data were in agreement with those reported in [6d]. $^1$H-NMR (400 MHz, $CDCl_3$): 7.48–7.28 (*m*, 5 arom. H); 4.71 (*t*, *J* = 7.8, H–C(2)); 4.57 (*d*, *J* = 11.7, 1 H of PhC$H_2$); 4.49 (*d*, *J* = 11.7, 1 H of PhC$H_2$); 4.20 (*dd*, *J* = 7.9, 4.1, H–C(4)); 4.05 (*dd*, *J* = 5.8, 3.1, H–C(3)); 3.52–3.42 (*m*, $CH_2$(6)); 2.58–2.35 (*m*, H–C(3)); 2.35–2.10 (*m*, H–C(3′)). $^{13}$C-NMR (101 MHz, $CDCl_3$): 175.7 (CO); 137.2 (1 arom. C); 128.6, 128.1, 127.7 (5 arom. CH); 83.6 (C(5)); 79.5 (C(4)); 76.5 (C(2)); 71.7 (Ph$CH_2$); 52.3 (C(6)); 36.0 (C(3)).

*General Peptide Synthesis.* a) *Stepwise Elongation for L-O-V-O-L:* Fmoc-Leucine preloaded HMPB-BHA resin (1.24 g, 0.81 mmol/g, 1 mmol) was submitted to four cycles of automated solid-phase synthesis using the Fmoc-based solid-phase peptide synthesis (SPPS) protocols with the building blocks in the order: Fmoc-Orn(Boc)-OH, Fmoc-Val-OH, Fmoc-Orn(Boc)-OH, and Fmoc-Leu-OH. The amino acids

were coupled with 3 equiv. HCTU and 3 equiv. of amino acid in 30 min. The resin was air-dried (1.57 g; loading 0.64 mmol/g).

b) *General Incorporation of Sugar Amino Acid* (SAA): *a*) The resin was washed with MeOH (2 × 10 ml), NMP (*N*-methylpyrrolidin-2-one; 2 × 10 ml), $CH_2Cl_2$ (2 × 10 ml); *b*) coupling of SAA to resin (for conditions: see exper. procedure for analogs **2**–**7**, **9**–**14**); *c*) washing with NMP (2 × 10 ml) and $CH_2Cl_2$ (2 × 10 ml).

c) *Reduction of $N_3$:* The resins were capped with $Ac_2O$ (5 equiv.), $EtN^iPr_2$ (5 equiv.) in 4 ml of NMP for 10 min. The resins were subsequently washed with 1,4-dioxane (3 × 10 ml) and taken up in 1,4-dioxane (10 ml) to which $Me_3P$ (16 equiv., 1M in THF), pre-mixed with $H_2O$ (0.6 equiv.), was added. The resin was shaken for 24 h; the reduction of the $N_3$ was monitored with the *Kaiser* test.

d) *Automated SPPS Elongation.* Azide-reduced resins were subjected to seven cycles of SPPS with the use of commercially available building blocks in the following order: Fmoc-Val-OH, Fmoc-L-Orn(Boc)-OH/Fmoc-D-Orn(Boc)-OH, Fmoc-Leu-OH, Fmoc-Orn(Boc)-OH, Fmoc-Leu-OH, Fmoc-Pro-OH, and Fmoc-D-Phe-OH, and subsequent Fmoc deprotection.

e) *Cleavage from Resin.* The peptides were released from the resin by mild acidic cleavage (4 × 10 min, 10 ml 1% TFA in $CH_2Cl_2$). The fractions were collected and co-evaporated with toluene (3 × 50 ml) to give the crude linear peptides which were immediately cyclized without further purification.

f) *Cyclization.* To a soln. of HOBt (5 equiv.), PyBOP (5 equiv.), and $EtN^iPr_2$ (15 equiv.) in DMF (160 ml) were dropwise added the crude peptides in DMF (20 ml) during 16 h using the syringe pump. The solvent was removed under reduced pressure, and the resulting mixture was applied to a *Sephadex®* size-exclusion column (50.0 mm × 1500 mm) and eluted with MeOH.

g) *Deprotection:* The Boc groups were removed by addition of TFA/TIS/$H_2O$ 95 : 2.5 : 2.5 (10 ml), and subsequently the peptides **2**–**7** and **9**–**14** were purified by prep. or semi-prep. RP-HPLC.

*cyclo[(3-OH)SAA$_4$-Leu-Orn-Val-Orn-Leu-$^D$Phe-Pro-Val-Orn-Leu-Orn-Val] TFA Salt* (= *3-[(3S,6S,9S,12S,15S,19R,20R,21R,24S,27S,30S,33S,36S,39R,44aS)-6,27,33-Tris(3-aminopropyl)-39-benzyl-tetratetracontahydro-20-hydroxy-9,24,36-tris(2-methylpropyl)-1,4,7,10,13,16,22,25,28,31,34,37,40-tridecaoxo-3,15,30-tri(propan-2-yl)-19,21-epoxypyrrolo[2,1-r][1,4,7,10,13,16,19,22,25,28,31,34,37]tridecaazacyclodotetracontin-12-yl]propan-1-aminium Trifluoroacetate*; **2**). Peptide **3** (20.65 mg, 10.26 μmol) was hydrogenated under $H_2$ in 1,4-dioxane (1 ml) and aq. HCl (0.7M, 1 ml) with Pd-black (20 mg). The mixture was filtered over *Celite®* yielding the crude peptide, which was purified by RP-HPLC (linear gradient of 38–47%, 3 column volumes (CVs)) to give **2** (15.71 mg, 80%). White amorphous powder. LC/MS: $t_R$ 4.75 min; linear gradient 10 → 90% *B* in 13.5 min; *m/z* 1467.3 ($[M+H]^+$). $^1$H-NMR (600 MHz, $CD_3OD$): 8.98 (*d*, *J* = 9.4, NH($Val_5$)); 8.93 (br. *s*, NH($^D$-$Phe_{13}$)); 8.73 (*d*, *J* = 9.1, NH($Leu_3$)); 8.65 (*d*, *J* = 9.0, NH($Leu_8$), NH($Orn_9$), NH($Leu_{12}$)); 8.62 (*d*, *J* = 8.9, NH($Orn_4$)); 8.53 (*d*, *J* = 8.8, NH($Orn_{11}$)); 8.44 (*d*, *J* = 9.2, NH($Orn_2$)); 8.01 (*t*, *J* = 5.6, NH(SAA)); 7.97 (br. *s*, $NH_2$(Orn)); 7.93 (*d*, *J* = 5.7, NH($Val_{10}$)); 7.75 (*d*, *J* = 8.6, NH($Val_1$)); 7.36–7.22 (*m*, 5 arom. H); 5.10 (*d*, *J* = 7.3, $H_\alpha$($Orn_{11}$)); 5.03–5.01 (*m*, $H_\alpha$($Orn_2$), $H_\alpha$($Orn_9$)); 4.97–4.91 (*m*, $H_\alpha$($Orn_4$)); 4.80–4.74 (*m*, 1 H); 4.72 (*d*, *J* = 6.4, 1 H); 4.70–4.61 (*m*, $H_\alpha$($Leu_3$), $H_\alpha$($Leu_{12}$)); 4.52 (*dt*, *J* = 10.9, 4.4, $H_\alpha$($^D$-$Phe_{13}$)); 4.41 (*dd*, *J* = 9.3, 7.2, $H_\alpha$($Leu_8$)); 4.37 (*d*, *J* = 6.7, $H_\alpha$($Pro_{14}$)); 4.25–4.19 (*m*, $H_\alpha$($Val_5$), $H_\alpha$($Val_{10}$)); 4.16 (br. *s*, 1 H); 4.12 (*t*, *J* = 8.6, $H_\alpha$($Val_1$)); 3.72 (*dd*, *J* = 12.8, 5.3, 1 H); 3.57–3.50 (*m*, 2 H); 3.13–3.00 (*m*, 2 H); 3.00–2.86 (*m*, 8 H); 2.49 (*q*, *J* = 8.9, 1 H); 2.30 (*dd*, *J* = 14.8, 6.9, 1 H); 2.13–2.03 (*m*, 1 H); 2.03–1.92 (*m*, 3 H); 1.88–1.41 (*m*, 23 H); 1.42–1.33 (*m*, 1 H); 1.05–0.75 (*m*, 36 H). $^{13}$C-NMR (151 MHz, $CD_3OH$): 174.6; 174.1; 174.0; 173.9; 173.7; 173.5; 173.4; 173.4; 172.9; 172.7; 172.6; 137.0; 130.5; 129.8; 128.6; 88.7; 85.4; 70.7; 62.1; 60.8; 59.1; 56.1; 53.7; 53.6; 53.6; 53.4; 52.7; 52.4; 51.8; 49.7; 48.0; 44.3; 42.2; 41.5; 41.4; 41.0; 40.8; 40.7; 37.4; 34.2; 31.9; 30.8; 30.7; 30.4; 30.3; 25.9; 25.9; 25.7; 25.7; 25.3; 25.1; 24.8; 24.6; 24.1; 23.3; 23.2; 23.2; 22.6; 21.9; 20.2; 19.9; 19.7; 19.6; 19.4; 19.0. HR-ESI-MS: 1466.9474 ($[M+H]^+$, $C_{72}H_{124}N_{17}O_{15}^+$; calc. 1466.9437).

*cyclo[(3-OBn)SAA$_4$-Leu-Orn-Val-Orn-Leu-$^D$Phe-Pro-Val-Orn-Leu-Orn-Val] TFA Salt* (= *3-[(3S,6S,9S,12R,15S,19R,24S,27S,30S,39R,44aS)-6,27,33-Tris(3-aminopropyl)-39-benzyl-20-(benzyloxy)-tetratetracontahydro-9,24,36-tris(2-methylpropyl)-1,4,7,10,13,16,22,25,28,31,34,37,40-tridecaoxo-3,15,30-tri(propan-2-yl)-19,21-epoxypyrrolo[2,1-r][1,4,7,10,13,16,19,22,25,28,31,34,37]tridecaazacyclodotetracontin-12-yl]propan-1-aminium Trifluoroacetate*; **3**). SAA **15** (105.3 mg, 2 equiv.) was pre-activated with HBTU (3 equiv., 3 ml of 0.2M HBTU in NMP) and $EtN^iPr_2$ (6 equiv., 199 μl) in 10 ml of NMP, and subsequently coupled to the resin **19** (498 mg, 0.2 mmol, 0.402 mmol/g) for 4 h (mini-cleavage from resin:

LC/MS: $t_R$ 6.21 min, linear gradient 10 → 90% *B* in 13.5 min; *m/z* 817.33 ($[M+H]^+$)). Resin **20** (0.1 mmol) was subjected to steps *c*–*g*, and the Boc-deprotected peptide was purified by RP-HPLC (linear gradient of 36–45%, 3 CV) and yielded **3** (40.6 mg, 20%). White amorphous powder. LC/MS: $t_R$ 6.13 min, linear gradient 10 → 90% *B* in 13.5 min; *m/z* 1557.3 ($[M+H]^+$). $^1$H-NMR (600 MHz, $CD_3OH$): 8.85 (*d*, *J* = 3.3, NH(D-Phe$_{13}$)); 8.66 (*d*, *J* = 8.7, NH(Val$_5$)); 8.55 (*d*, *J* = 10.0, NH(Leu$_{12}$)); 8.53 (*d*, *J* = 8.8, NH(Leu$_5$)); 8.53 (*d*, *J* = 8.9, NH(Orn$_{11}$)); 8.49 (*d*, *J* = 8.2, NH(Orn$_9$)); 8.47 (*d*, *J* = 10.0, NH(Val$_{10}$)); 8.40 (*d*, *J* = 8.3, NH(Orn$_2$), NH(Orn$_4$)); 8.13 (*t*, *J* = 5.5, NH(SAA$_4$)); 8.06 (*d*, *J* = 6.2, NH(Leu$_8$)); 7.93 (br. *s*, $NH_2$(Orn)); 7.83 (br. *s*, $NH_2$(Orn)); 7.78 (*d*, *J* = 8.2, NH(Val$_1$)); 7.40–7.21 (*m*, 10 H); 4.93–4.83 (*m*, $H_\alpha$(Orn$_2$), $H_\alpha$(Orn$_9$), $H_\alpha$(Orn$_{11}$)); 4.79–4.77 (*m*, $H_\alpha$(Orn$_4$)); 4.62–4.54 (*m*, $H_\alpha$(Leu$_3$), $H_\alpha$(Leu$_{12}$), 1 H of PhC$H_2$, $H_\alpha$(D-Phe$_{13}$)); 4.43 (*d*, *J* = 11.6, 1 H of PhC$H_2$); 4.36–4.34 (*m*, $H_\alpha$(Pro$_{14}$), $H_\alpha$(Val$_{10}$)); 4.32–4.28 (*m*, $H_\alpha$(Leu$_8$)); 4.25–4.20 (*m*, $H_\alpha$(Val$_5$)); 4.05 (*t*, *J* = 8.4, $H_\alpha$(Val$_1$)); 3.72–3.69 (*m*, 1 H); 3.50–3.47 (*m*, 1 H); 3.41–3.39 (*m*, 1 H); 3.07–3.02 (*m*, 2 H); 2.99–2.89 (*m*, 8 H); 2.78–2.76 (*m*, 1 H); 2.55 (*q*, *J* = 8.3, 1 H); 2.29–2.24 (*m*, 1 H); 2.10–1.87 (*m*, 3 H); 1.87–1.45 (*m*, 23 H); 1.39–1.35 (*m*, 1 H); 0.98 (*d*, *J* = 4.9, 3 H); 0.97 (*d*, *J* = 5.2, 3 H); 0.94–0.85 (*m*, 27 H); 0.83 (*d*, *J* = 6.1, 3 H). $^{13}$C-NMR (151 MHz, $CD_3OH$): 174.7; 174.5; 174.1; 173.8; 173.6; 173.5; 173.1; 172.9; 172.9; 172.7; 138.5; 137.1; 130.5; 129.8; 129.7; 129.3; 128.9; 128.6; 86.3; 83.2; 77.4; 72.4; 62.0; 61.1; 60.9; 59.6; 55.9; 54.2; 53.8; 53.6; 53.3; 52.9; 51.9; 48.1; 43.6; 42.3; 42.2; 41.6; 40.9; 40.9; 40.7; 40.6; 37.6; 33.7; 31.6; 30.9; 30.8; 30.7; 30.6; 30.4; 30.0; 25.9; 25.9; 25.8; 25.3; 25.2; 24.8; 24.7; 24.1; 23.5; 23.2; 23.0; 22.4; 21.8; 20.0; 20.0; 19.8; 19.7; 19.5; 19.1. HR-ESI-MS: 1556.9925 ($[M+H]^+$, $C_{79}H_{130}N_{17}O_{15}^+$; calc. 1556.9927).

*cyclo[(3-OH)SAA$_5$-Leu-Orn-Val-Orn-Leu-*D*Phe-Pro-Val-Orn-Leu-Orn-Val] TFA Salt* (= *3-[(3*S*,6*S*,9*S*,12*R*,15*S*,19*R*,20*R*,22*R*,25*S*,28*S*,31*S*,40*R*,45a*S*)-6,28,34-Tris(3-aminopropyl)-40-benzyltetratetracontahydro-20-hydroxy-9,25,37-tris(2-methylpropyl)-1,4,7,10,13,16,23,26,29,32,35,38,41-tridecaoxo-3,15,31-tri(propan-2-yl)-1 H-19,22-epoxypyrrolo[2,1-*r*][1,4,7,10,13,16,19,22,25,28,31,34,37]tridecaazacyclotritetracontin-12-yl]propan-1-aminium Trifluoroacetate*; **4**). SAA **16a** (28.1 mg, 1.5 equiv.) was pre-activated with HCTU (1.4 equiv., 57.9 mg) and EtN$^i$Pr$_2$ (2.8 equiv., 46 µl) in 10 ml of NMP, and subsequently coupled to the resin **19** (200 mg, 0.1 mmol, 0.5 mmol/g) for 4 h (mini-cleavage: LC/MS $t_R$ 5.14 min, linear gradient 10 → 90% *B* in 13.5 min; *m/z* 741.33 ($[M+H]^+$)). The resin (0.1 mmol) was subjected to steps *c*–*g*, and Boc-deprotected peptide was purified by RP-HPLC (linear gradient of 38–47%, 3 CV) and yielded **4** (12.0 mg, 6.2 µmol, 6.2%). White amorphous powder. LC/MS: $t_R$ 5.81 min, linear gradient 10 → 90% *B* in 13.5 min; *m/z* 1482.3 ($[M+H]^+$). $^1$H-NMR (600 MHz, $CD_3OH$): 9.05 (*d*, *J* = 9.6, NH(Val$_5$)); 8.94 (*d*, *J* = 3.1, NH(D-Phe$_{13}$)); 8.78 (*d*, *J* = 9.1, NH(Leu$_3$)); 8.66 (*d*, *J* = 8.4, NH(Orn$_9$)); 8.65 (*d*, *J* = 7.5, NH(Leu$_{12}$)); 8.62 (*d*, *J* = 9.6, NH(Leu$_8$)); 8.54 (*d*, *J* = 8.4, NH(Orn$_{11}$)); 8.48 (br. *s*, 1 H of $NH_2$(Orn)); 8.45 (*d*, *J* = 8.5, NH(Orn$_4$)); 8.43 (*d*, *J* = 8.0, NH(Orn$_2$)); 8.28 (*t*, *J* = 6.2, NH(SAA$_5$)); 8.01 (*d*, *J* = 6.4, NH(Val$_{10}$)); 7.92 (br. *s*, $NH_2$(Orn)); 7.76 (*d*, *J* = 8.6, NH(Val$_1$)); 7.37–7.18 (*m*, 5 H); 5.12–5.08 (*m*, $H_\alpha$(Orn$_4$), $H_\alpha$(Orn$_{11}$)); 5.08–5.00 (*m*, $H_\alpha$(Orn$_2$), $H_\alpha$(Orn$_9$)): 4.68–4.65 (*m*, $H_\alpha$(Leu$_3$), $H_\alpha$(Leu$_{12}$)); 4.57–4.48 (*m*, $H_\alpha$(D-Phe$_{13}$)); 4.42 (*dd*, *J* = 10.8, 5.4, 1 H); 4.38–4.35 (*m*, $H_\alpha$(Pro$_{14}$), $H_\alpha$(Leu$_8$)); 4.27–4.15 (*m*, $H_\alpha$(Val$_{10}$)); 4.11–4.09 (*m*, $H_\alpha$(Val$_1$), $H_\alpha$(Val$_5$)); 4.07–4.05 (*m*, 1 H); 3.91 (*dd*, *J* = 13.9, 7.0, 1 H); 3.73 (*dd*, *J* = 12.5, 5.4, 1 H); 3.10–3.05 (*m*, 3 H); 3.00–2.83 (*m*, 8 H); 2.48 (*d*, *J* = 8.1, 1 H); 2.30 (*dd*, *J* = 15.0, 6.9, 1 H); 2.09 (*dd*, *J* = 11.8, 5.6, 1 H); 2.05–1.28 (*m*, 32 H); 1.08–0.70 (*m*, 36 H). $^{13}$C-NMR (151 MHz, $CD_3OH$): 175.2; 175.2; 174.3; 173.9; 173.7; 173.7; 173.7; 173.6; 173.5; 173.4; 172.9; 172.8; 172.6; 163.2; 163.0; 137.0; 130.5; 129.8; 128.6; 89.5; 79.1; 73.6; 62.1; 60.9; 60.6; 59.4; 56.1; 54.1; 53.4; 53.2; 52.7; 52.4; 51.8; 49.7; 47.9; 44.6; 42.2; 42.1; 41.9; 41.4; 40.7; 37.4; 34.3; 31.8; 31.7; 30.7; 30.5; 29.6; 25.9; 25.7; 25.4; 25.2; 24.8; 24.6; 24.3; 23.5; 23.2; 23.1; 22.5; 21.8; 19.9; 19.7; 19.7; 19.3; 19.3. HR-ESI-MS: 1480.9633 ($[M+H]^+$, $C_{73}H_{126}N_{17}O_{15}^+$; calc. 1480.9614).

*cyclo[(3-OBn)SAA$_5$-Leu-Orn-Val-Orn-Leu-*D*Phe-Pro-Val-Orn-Leu-Orn-Val] TFA Salt* (= *3-[(3*S*,6*S*,9*S*,12*R*,15*S*,19*R*,20*R*,22*R*,25*S*,28*S*,31*S*,40*R*,45a*S*)-6,28,34-Tris(3-aminopropyl)-40-benzyl-20-(benzyloxy)tetratetracontahydro-9,25,37-tris(2-methylpropyl)-1,4,7,10,13,16,23,26,29,32,35,38,41-tridecaoxo-3,15,31-tri(propan-2-yl)-1*H*-19,22-epoxypyrrolo[2,1-*r*][1,4,7,10,13,16,19,22,25,28,31,34,37]tridecaazacyclotritetracontin-12-yl]propan-1-aminium Trifluoroacetate*; **5**). SAA **16b** (33.2 mg, 1.2 equiv.) was pre-activated with HCTU (1.2 equiv., 50 mg) and EtN$^i$Pr$_2$ (3 equiv., 60 µl) in 10 ml of NMP, and subsequently coupled to the resin **19** (200 mg, 0.1 mmol, 0.5 mmol/g) for 4 h (mini-cleavage: LC/MS: $t_R$ 6.31 min, linear gradient 10 → 90% *B* in 13.5 min; *m/z* 831.53 ($[M+H]^+$)). The resin (0.05 mmol) was subjected to steps *c*–*g*, and Boc-deprotected peptide was purified by RP-HPLC (linear gradient of 43–

52%, 3 CV) to yield **5** (11.84 mg, 5.84 μmol, 12%). White amorphous powder. LC/MS: $t_R$ 6.39 min, linear gradient 10 → 90% *B* in 13.5 min; *m/z* 1571.5 ($[M+H]^+$). $^1$H-NMR (600 MHz, $CD_3OH$): 9.04 (*d*, *J* = 9.6, NH($Val_5$)); 8.94 (*s*, NH(D-$Phe_{13}$)); 8.76 (*d*, *J* = 9.0, NH($Leu_3$)); 8.65 (*d*, *J* = 7.6, NH($Orn_{11}$)); 8.64 (*d*, *J* = 7.7, NH($Leu_{12}$)); 8.63 (*d*, *J* = 9.3, NH($Val_{10}$)); 8.55 (*d*, *J* = 8.1, NH($Orn_9$)); 8.43 (*d*, *J* = 9.2, NH($Orn_2$), NH($Orn_4$)); 8.33 (*t*, *J* = 5.9, NH(SAA)); 8.01 (*d*, *J* = 6.3, NH($Leu_8$)); 7.92 (br. *s*, $NH_2$(Orn)); 7.77 (*d*, *J* = 8.6, NH($Val_1$)); 7.41–7.20 (*m*, 10 H); 5.14–5.12 (*m*, $H_\alpha$($Orn_4$)); 5.09–4.99 (*m*, $H_\alpha$($Orn_2$), $H_\alpha$($Orn_{11}$)); 4.88 (*m*, $H_\alpha$($Orn_9$)); 4.72–4.61 (*m*, $H_\alpha$($Leu_3$), $H_\alpha$($Leu_{12}$)); 4.57–4.50 (*m*, $H_\alpha$(D-$Phe_{13}$)); 4.39–4.37 (*m*, $H_\alpha$(Pro), $H_\alpha$($Val_{10}$), 1 H of PhC$H_2$); 4.28 (*s*, 1 H); 4.19 (*dt*, *J* = 10.9, 5.5, $H_\alpha$($Leu_8$)); 4.15–4.05 (*m*, $H_\alpha$($Val_1$), $H_\alpha$($Val_5$), 1 H of PhC$H_2$); 3.94 (*dd*, *J* = 13.8, 7.0, 1 H); 3.73 (*dd*, *J* = 12.8, 5.3, 1 H); 3.15–3.01 (*m*, 3 H); 3.00–2.78 (*m*, 8 H); 2.49 (*q*, *J* = 8.9, 1 H); 2.37–2.24 (*m*, 2 H); 2.05–1.25 (*m*, 32 H); 1.04–0.71 (*m*, 36 H). $^{13}$C-NMR (151 MHz, $CD_3OH$): 175.2; 174.9; 174.3; 174.0; 173.7; 173.7; 173.6; 173.6; 173.5; 173.4; 172.8; 172.8; 172.6; 163.3; 163.0; 139.3; 137.0; 130.5; 129.8; 129.6; 129.0; 128.9; 128.6; 87.2; 81.8; 79.4; 72.2; 62.0; 60.9; 60.6; 59.4; 56.1; 54.2; 53.3; 53.1; 52.7; 52.4; 51.8; 49.8; 47.9; 44.7; 42.6; 42.2; 41.4; 41.0; 40.8; 40.8; 40.7; 39.3; 37.4; 34.3; 31.8; 31.8; 30.7; 30.7; 30.5; 29.5; 25.9; 25.7; 25.4; 25.3; 25.1; 24.8; 24.6; 24.3; 23.5; 23.2; 23.1; 22.4; 21.8; 20.0; 19.7; 19.7; 19.6; 19.3; 19.3. HR-ESI-MS: 11571.0108 ($[M+H]^+$, $C_{80}H_{132}N_{17}O_{15}^+$; calc. 1571.0083).

*cyclo[(3-OH)SAA$_6$-Leu-Orn-Val-Orn-Leu-*D*-Phe-Pro-Val-Orn-Leu-Orn-Val] TFA Salt* (= *3-[(3*S*,6*S*,9*S*,12*R*,15*S*,19*R*,20*R*,23*R*,26*S*,29*S*,32*S*,41*R*,46a*S*)-6,29,35-Tris(3-aminopropyl)-41-benzylhexatetracontahydro-20-hydroxy-9,26,38-tris(2-methylpropyl)-1,4,7,10,13,16,24,27,30,33,36,39,42-tridecaoxo-3,15,32-tri(propan-2-yl)-19,23-epoxypyrrolo[2,1-r][1,4,7,10,13,16,19,22,25,28,31,34,37]tridecaazacyclotetratetracontin-12-yl]propan-1-aminium trifluoroacetate*; **6**). SAA **18a** (62.4 mg, 1.55 equiv.) was preactivated with HCTU (1.45 equiv., 120 mg) and EtN$^i$Pr$_2$ (2.9 equiv., 96 μl) in 10 ml of NMP, and subsequently coupled to the resin **19** (400 mg, 0.2 mmol, 0.5 mmol/g) for 4 h (mini-cleavage LC/MS: $t_R$ 5.28 min, linear gradient 10 → 90% *B* in 13.5 min; *m/z* 755.33 ($[M+H]^+$)). The resin (0.1 mmol) was subjected to steps *c*–*g*, and Boc-deprotected peptide was purified by RP-HPLC (linear gradient of 37–46%, 3 CV) to yield **6** (1.8 mg, 0.9 μmol, 1%). White amorphous powder. LC/MS: $t_R$ 5.77 min, linear gradient 10 → 90% *B* in 13.5 min; *m/z* 1495.3 ($[M+H]^+$). $^1$H-NMR (600 MHz, $CD_3OH$): 8.92 (*d*, *J* = 3.2, NH(D-$Phe_{13}$)); 8.74 (*d*, *J* = 8.9, NH($Leu_8$)); 8.63 (*d*, *J* = 8.3, NH($Orn_{11}$)); 8.62 (*d*, *J* = 8.5, NH($Leu_{12}$)); 8.61 (*d*, *J* = 9.3, NH($Val_5$), NH($Val_{10}$)); 8.53 (*d*, *J* = 8.3, NH($Orn_4$)); 8.42 (*t*, *J* = 9.0, NH($Orn_2$), NH($Orn_9$)); 8.09 (*d*, *J* = 8.5, NH($Leu_3$), NH($SAA_6$)); 7.77 (*d*, *J* = 8.5, NH($Val_1$)); 7.38–7.21 (*m*, 5 H); 5.11–5.10 (*m*, $H_\alpha$($Orn_9$)); 5.04–5.01 (*m*, $H_\alpha$($Orn_2$), $H_\alpha$($Orn_{11}$)); 4.87–4.85 (*m*, $H_\alpha$($Orn_4$)); 4.67–4.64 (*m*, $H_\alpha$($Leu_8$), $H_\alpha$($Leu_{12}$)); 4.53 (*dd*, *J* = 10.7, 4.6, $H_\alpha$(D-$Phe_{13}$)); 4.50–4.40 (*m*, $H_\alpha$($Leu_3$), 1 H of PhC$H_2$); 4.39–4.32 (*m*, $H_\alpha$($Pro_{14}$), $H_\alpha$($Val_{10}$)); 4.15 (*t*, *J* = 9.4, $H_\alpha$($Val_5$)); 4.11 (*t*, *J* = 8.4, $H_\alpha$($Val_1$)); 3.94–3.90 (*m*, 2 H); 3.73 (*t*, *J* = 9.0, 1 H); 3.37–3.18 (*m*, 3 H); 3.12–3.01 (*m*, 2 H); 3.01–2.78 (*m*, 8 H); 2.50 (*dd*, *J* = 17.2, 8.2, 1 H); 2.30 (*dd*, *J* = 14.6, 7.0, 1 H); 2.14–1.90 (*m*, 6 H); 1.86–1.44 (*m*, 26 H); 1.43–1.30 (*m*, 1 H); 1.18–1.12 (*m*, 1 H); 1.06–0.71 (*m*, 36 H). $^{13}$C-NMR (151 MHz, $CD_3OH$): 175.2; 174.3; 174.2; 174.1; 174.0; 173.7; 173.5; 172.9; 172.6; 163.2; 137.0; 130.5; 129.8; 128.6; 81.7; 75.8; 66.1; 62.0; 60.9; 59.4; 56.1; 54.1; 53.4; 52.7; 52.6; 52.4; 51.8; 48.0; 42.3; 42.1; 41.0; 40.9; 40.7; 40.1; 37.4; 34.2; 32.5; 31.9; 31.8; 30.9; 30.7; 29.8; 29.6; 25.9; 25.9; 25.7; 25.3; 24.9; 24.6; 24.3; 23.4; 23.2; 23.1; 22.5; 21.9; 20.0; 19.8; 19.7; 19.6; 19.3. HR-ESI-MS: 747.9920 ($[M+H]^{2+}$, $C_{74}H_{129}N_{17}O_{15}^+$; calc. 747.9922).

*cyclo[(3-OBn)SAA$_6$-Leu-Orn-Val-Orn-Leu-*D*-Phe-Pro-Val-Orn-Leu-Orn-Val] TFA Salt* (= *3-[(3*S*,6*S*,9*S*,12*R*,15*S*,19*R*,20*R*,23*R*,26*S*,29*S*,32*S*,41*R*,46a*S*)-6,29,35-Tris(3-aminopropyl)-41-benzyl-20-(benzyloxy)hexatetracontahydro-9,26,38-tris(2-methylpropyl)-1,4,7,10,13,16,24,27,30,33,36,39,42-tridecaoxo-3,15,32-tri(propan-2-yl)-19,23-epoxypyrrolo[2,1-r][1,4,7,10,13,16,19,22,25,28,31,34,37]tridecaazacyclotetratetracontin-12-yl]propan-1-aminium trifluoroacetate*; **7**). SAA **18b** (44 mg, 1.5 equiv.) was preactivated with HCTU (1. 5 equiv., 63 mg) and EtN$^i$Pr$_2$ (3 equiv., 50 μl) in 10 ml of NMP, and subsequently coupled to the resin **19** (200 mg, 0.1 mmol, 0.5 mmol/g) for 4 h (LC/MS: $t_R$ 6.68 min, linear gradient 10 → 90% *B* in 13.5 min; *m/z* 845.33 ($[M+H]^+$)). The resin (0.1 mmol) was subjected to steps *c*–*g*, and Boc-deprotected peptide was purified by RP-HPLC (linear gradient of 43–52%, 3 CV) to yield **7** (14.3 mg, 7.0 μmol, 7%). White amorphous powder. LC/MS: $t_R$ 6.51 min, linear gradient 10 → 90% *B* in 13.5 min; *m/z* 1585.4 ($[M+H]^+$). $^1$H-NMR (600 MHz, $CD_3OH$): 8.92 (*d*, *J* = 3.3, NH(D-$Phe_{13}$)); 8.73 (*d*, *J* = 8.9, NH($Leu_3$)); 8.63 (*d*, *J* = 8.9, NH($Val_{10}$), NH($Leu_{12}$)); 8.61 (*d*, *J* = 9.2, NH($Orn_{11}$), NH($Val_5$)); 8.53 (*d*, *J* = 8.2, NH($Orn_9$)); 8.42 (*d*, *J* = 9.2, NH($Orn_2$), NH($Orn_4$)); 8.11 (*d*, *J* = 8.4, NH($Leu_8$)); 7.92 (*t*, *J* = 6.1,

NH(SAA)); 7.77 (*d*, *J* = 8.5, NH($Val_1$)); 7.40–7.22 (*m*, 10 H); 5.09 (*t*, *J* = 7.0, $H_\alpha$($Orn_4$)); 5.04–5.02 (*m*, $H_\alpha$($Orn_2$), $H_\alpha$($Orn_{11}$)); 4.87–4.83 (*m*, $H_\alpha$($Orn_9$)); 4.73–4.60 (*m*, $H_\alpha$($Leu_3$), $H_\alpha$($Leu_{12}$), 1 H of PhC$H_2$); 4.58–4.49 (*m*, $H_\alpha$(D-$Phe_{13}$), 1 H of PhC$H_2$); 4.44–4.42 (*m*, $H_\alpha$($Leu_8$)); 4.37–4.36 (*m*, $H_\alpha$($Pro_{14}$), $H_\alpha$($Val_{10}$)); 4.15 (*t*, *J* = 9.4, $H_\alpha$($Val_5$)); 4.11 (*t*, *J* = 8.5, $H_\alpha$($Val_1$)); 3.96–3.87 (*m*, 2 H); 3.73 (*dd*, *J* = 12.7, 5.3, 1 H); 3.46 (*d*, *J* = 9.3, 1 H); 3.27–3.16 (*m*, 2 H); 3.16–3.01 (*m*, 3 H); 3.01–2.89 (*m*, 6 H); 2.84 (*s*, 2 H); 2.49 (*t*, *J* = 8.5, 1 H); 2.38–2.24 (*m*, 2 H); 2.10 (*dd*, *J* = 13.3, 2.7, 1 H); 2.08–1.90 (*m*, 4 H); 1.86–1.43 (*m*, 26 H); 1.41–1.25 (*m*, 1 H); 1.12 (*d*, *J* = 14.7, 1 H); 1.03–0.74 (*m*, 36 H). $^{13}$C-NMR (151 MHz, $CD_3OH$): 175.2; 174.3; 174.1; 174.0; 174.0; 173.7; 173.7; 173.5; 173.4; 172.9; 172.8; 172.6; 139.9; 137.0; 130.5; 129.8; 129.5; 129.0; 128.9; 128.6; 80.1; 75.9; 73.5; 71.8; 62.0; 60.9; 60.9; 59.4; 56.1; 54.2; 53.4; 53.4; 52.7; 52.6; 52.5; 51.8; 49.7; 48.0; 42.3; 42.1; 41.0; 40.8; 40.2; 37.4; 34.1; 31.9; 31.8; 30.9; 30.8; 30.7; 29.6; 29.3; 29.0; 25.9; 25.9; 25.7; 25.2; 24.8; 24.6; 24.3; 23.4; 23.2; 23.1; 22.6; 21.9; 20.0; 19.8; 19.7; 19.6; 19.3. HR-ESI-MS: 1585.0258 ($[M+H]^+$, $C_{81}H_{134}N_{17}O_{15}^+$; calc. 1585.0240).

*cyclo[(3-OH)SAA$_4$-Leu-Orn-Val-Orn-Leu-*D*Phe-Pro-Val-Orn-Leu-*D*Orn-Val] TFA Salt* (= *3-[(3S,6S,9S,12S,15S,19R,24S,27S,30S,39R,44aS)-6,27,33-Tris(3-aminopropyl)-39-benzyltetratetracontahydro-20-hydroxy-9,24,36-tris(2-methylpropyl)-1,4,7,10,13,16,22,25,28,31,34,37,40-tridecaoxo-3,15,30-tri(propan-2-yl)-19,21-epoxypyrrolo[2,1-r][1,4,7,10,13,16,19,22,25,28,31,34,37]tridecaazacyclodotetracontin-12-yl]propan-1-aminium Trifluoroacetate*; **9**). Peptide **10** (18.51 mg, 9.19 μmol) was hydrogenated under $H_2$ in 1,4-dioxane (1 ml) and aq. HCl (0.7M, 1 ml) with Pd-black (20 mg). The mixture was filtered over *Celite*® to yield the crude peptide, which was purified by RP-HPLC (linear gradient of 31–40%, 3 CV) to give **9** (5.74 mg, 2.98 μmol, 32%). White amorphous powder. LC/MS: $t_R$ 4.96 min, linear gradient 10 → 90% *B* in 13.5 min; *m*/*z* 1467.3 ($[M+H]^+$). $^1$H-NMR (600 MHz, $CD_3OH$): 8.81 (*d*, *J* = 3.9, NH(D-$Phe_{13}$)); 8.55 (*d*, *J* = 8.4, NH($Orn_2$)); 8.54 (*d*, *J* = 7.7, NH($Orn_9$)); 8.45 (*d*, *J* = 8.3, NH($Orn_{11}$)); 8.42 (*d*, *J* = 8.8, NH($Leu_{12}$)); 8.33 (*d*, *J* = 8.3, NH($Leu_8$), NH($SAA_4$)); 8.30 (*d*, *J* = 8.0, NH($Leu_3$)); 8.24 (*d*, *J* = 8.2, NH($Val_5$)); 7.98 (*d*, *J* = 8.4, NH($Val_{10}$)); 7.94 (*d*, *J* = 7.8, NH($Orn_4$)); 7.86 (*d*, *J* = 8.0, NH($Val_1$)); 7.85 (br. *s*, $NH_2$(Orn)); 7.32–7.24 (*m*, 5 H); 4.82–4.78 (*m*, $H_\alpha$($Orn_{11}$)); 4.72 (*d*, *J* = 4.6, 1 H); 4.63–4.46 (*m*, $H_\alpha$(D-$Phe_{13}$), $H_\alpha$($Orn_2$), $H_\alpha$($Orn_4$), $H_\alpha$($Orn_9$), $H_\alpha$($Leu_3$), $H_\alpha$($Leu_8$), $H_\alpha$($Leu_{12}$)); 4.41–4.34 (*m*, $H_\alpha$($Pro_{14}$)); 4.32 (*t*, *J* = 7.4, $H_\alpha$($Val_5$)); 4.26 (*t*, *J* = 7.9, $H_\alpha$($Val_{10}$)); 4.21 (*t*, *J* = 4.3, 1 H); 4.06–3.95 (*m*, $H_\alpha$($Val_1$)); 3.72–3.69 (*m*, 1 H); 3.65 (*s*, 1 H); 3.21–3.14 (*m*, 2 H); 3.06 (*dd*, *J* = 12.8, 5.7, 1 H); 3.03–2.90 (*m*, 9 H); 2.63 (*dd*, *J* = 17.9, 9.4, 1 H); 2.26 (*td*, *J* = 13.6, 6.8, 1 H); 1.95–1.49 (*m*, 29 H); 1.44–1.35 (*m*, 2 H); 1.06–0.82 (*m*, 36 H). $^{13}$C-NMR (151 MHz, $CD_3OH$): 175.3; 174.6; 174.3; 174.2; 174.0; 173.8; 173.6; 173.5; 173.5; 173.4; 172.8; 163.1; 162.9; 137.2; 130.5; 129.8; 128.5; 89.1; 86.1; 72.8; 64.6; 61.9; 61.3; 60.3; 55.7; 54.4; 54.1; 53.7; 53.4; 53.4; 52.9; 52.3; 49.7; 48.1; 43.2; 42.3; 41.9; 41.8; 40.9; 40.7; 40.5; 37.7; 32.3; 32.2; 31.5; 31.1; 30.7; 29.8; 29.6; 26.2; 26.0; 25.4; 25.2; 25.1; 24.8; 24.7; 23.8; 23.6; 23.0; 22.0; 21.7; 20.2; 19.9; 19.8; 19.7; 18.9; 18.8. HR-ESI-MS: 11466.9469 ($[M+H]^+$, $C_{72}H_{124}N_{17}O_{15}^+$; calc. 1466.9457).

*cyclo[(3-OBn)SAA$_4$-Leu-Orn-Val-Orn-Leu-*D*Phe-Pro-Val-Orn-Leu-*D*Orn-Val] TFA Salt* (= *3-[(3S,6S,9S,12S,15S,19R,24S,27S,30S,39R,44aS)-6,27,33-Tris(3-aminopropyl)-39-benzyl-20-(benzyloxy)tetratetracontahydro-9,24,36-tris(2-methylpropyl)-1,4,7,10,13,16,22,25,28,31,34,37,40-tridecaoxo-3,15,30-tri-(propan-2-yl)-19,21-epoxypyrrolo[2,1-r][1,4,7,10,13,16,19,22,25,28,31,34,37]tridecaazacyclodotetracontin-12-yl]propan-1-aminium Trifluoroacetate*; **10**). SAA **15** (105.3 mg, 2 equiv.) was pre-activated with HBTU (3 equiv., 3 ml of 0.2M HBTU in NMP) and Et$N^iPr_2$ (6 equiv., 199 μl) in 10 ml of NMP, and subsequently coupled to the L-O-V-DO-L resin (498 mg, 0.2 mmol, 0.402 mmol/g) for 4 h (mini-cleavage: LC/MS: $t_R$ 6.21 min, linear gradient 10 → 90% *B* in 13.5 min; *m*/*z* 817.33 ($[M+H]^+$)). The resin (0.1 mmol) was subjected to *c*–*g*, and Boc-deprotected peptide was purified by RP-HPLC (linear gradient of 34–43%, 3 CV) to give **10** (45.2 mg, 22.5 μmol, 23%). White amorphous powder. LC/MS: $t_R$ 5.90 min, linear gradient 10 → 90% *B* in 13.5 min; *m*/*z* 1558.3 ($[M+H]^+$). $^1$H-NMR (600 MHz, $CD_3OH$): 8.87 (*d*, *J* = 3.8, NH(D-$Phe_{13}$)); 8.60 (*d*, *J* = 7.9, NH($Orn_2$)); 8.53 (*d*, *J* = 6.9, NH($Orn_9$)); 8.47 (*d*, *J* = 8.4, NH($Leu_{12}$)); 8.46 (*d*, *J* = 6.8, NH($Orn_{11}$)); 8.33 (*d*, *J* = 9.6, NH($Leu_3$), NH($Leu_8$), NH($SAA_4$)); 8.25 (*d*, *J* = 8.5, NH($Val_{10}$)); 8.08 (*d*, *J* = 8.6, NH($Val_5$)); 7.87 (*d*, *J* = 8.0, NH($Val_1$)); 7.81 (*d*, *J* = 7.8, NH($Orn_4$)); 7.38–7.20 (*m*, 10 H); 4.71–4.33 (*m*, PhC$H_2$, $H_\alpha$(D-$Phe_{13}$), $H_\alpha$($Orn_2$), $H_\alpha$($Orn_4$), $H_\alpha$($Orn_9$), $H_\alpha$($Orn_{11}$), $H_\alpha$($Leu_3$), $H_\alpha$($Leu_8$), $H_\alpha$($Leu_{12}$), $H_\alpha$($Val_{10}$), $H_\alpha$($Pro_{14}$)); 4.26 (*t*, *J* = 8.2, $H_\alpha$($Val_5$)); 4.15 (*t*, *J* = 4.2, 1 H); 4.05–3.99 (*m*, $H_\alpha$($Val_1$)); 3.70 (*d*, *J* = 7.1, 1 H); 3.16–3.04 (*m*, 2 H); 3.04–2.90 (*m*, 10 H); 2.58 (*d*, *J* = 8.1, 1 H); 2.27 (*dd*, *J* = 15.4, 6.8, 1 H); 2.06–1.48 (*m*, 30 H); 1.40 (*dd*, *J* = 13.0, 6.6, 1 H); 1.00–0.88 (*m*, 36 H). $^{13}$C-NMR (151 MHz, $CD_3OH$): 175.3; 174.6; 174.3; 174.1; 174.0; 173.9; 173.8; 173.6; 173.5;

172.8; 172.7; 138.5; 137.2; 130.5; 129.8; 129.5; 129.2; 129.1; 128.6; 86.7; 84.0; 78.6; 72.3; 61.9; 61.3; 60.3; 59.9; 55.8; 54.7; 54.2; 53.6; 53.4; 53.2; 52.6; 52.2; 48.0; 43.0; 42.4; 41.9; 41.8; 40.9; 40.7; 40.7; 40.5; 37.6; 32.5; 32.2; 31.8; 31.4; 31.3; 30.7; 29.5; 26.2; 26.0; 26.0; 25.5; 25.2; 24.7; 24.6; 23.8; 23.7; 23.1; 23.0; 21.9; 21.6; 20.2; 19.9; 19.7; 18.9; 18.8. HR-ESI-MS: 1556.9934 ($[M+H]^+$, $C_{79}H_{130}N_{17}O_{15}^+$; calc. 1556.9927).

*cyclo[(3-OH)SAA$_5$-Leu-Orn-Val-Orn-Leu-$^D$Phe-Pro-Val-Orn-Leu-$^D$Orn-Val] TFA Salt* (= *3-[(3S,6S,9S,12S,15S,19R,20R,22R,25S,28S,31S,40R,45aS)-6,28,34-Tris(3-aminopropyl)-40-benzyltetratetracontahydro-20-hydroxy-9,25,37-tris(2-methylpropyl)-1,4,7,10,13,16,23,26,29,32,35,38,41-tridecaoxo-3,15,31-tri(propan-2-yl)-1*H*-19,22-epoxypyrrolo[2,1-r][1,4,7,10,13,16,19,22,25,28,31,34,37]tridecaazacyclotritetracontin-12-yl]propan-1-aminium Trifluoroacetate*; **11**). SAA **16a** (30 mg, 1.6 equiv.) was pre-activated with HCTU (1.6 equiv., 66 mg), and Et$N^iPr_2$ (3 equiv., 53 µl) in 10 ml of NMP, and subsequently coupled to the L-O-V-$^D$O-L resin (200 mg, 0.1 mmol, 0.5 mmol/g) for 4 h (mini-cleavage: LC/MS: $t_R$ 5.14 min, linear gradient 10 → 90% *B* in 13.5 min; *m/z* 741.33 ($[M+H]^+$)). The resin (0.1 mmol) was subjected to steps *c*–*g*, and the Boc-deprotected peptide was purified by RP-HPLC (linear gradient of 29–38%, 3 CV) to give **11** (9.11 mg, 4.70 µmol, 5%). White amorphous powder. LC/MS: $t_R$ 4.89 min, linear gradient 10 → 90% *B* in 13.5 min; *m/z* 1482.1 ($[M+H]^+$). $^1$H-NMR (600 MHz, $CD_3OH$): 8.83 (*d*, *J* = 2.7, NH(D-Phe$_{13}$)); 8.55 (*d*, *J* = 8.3, NH(Orn$_9$)); 8.52 (*d*, *J* = 8.6, NH(Orn$_2$)); 8.49 (*d*, *J* = 8.4, NH(Orn$_{11}$)); 8.46 (*d*, *J* = 8.9, NH(Leu$_{12}$)); 8.44 (*t*, *J* = 4.7, NH(SAA)); 8.34 (*d*, *J* = 8.3, NH(Leu$_3$)); 8.21 (*d*, *J* = 7.7, NH(Val$_{10}$)); 8.20 (*d*, *J* = 8.3, NH(Leu$_8$)); 8.14 (*d*, *J* = 7.8, NH(Orn$_4$)); 8.07 (*d*, *J* = 8.5, NH(Val$_5$)); 7.85 (br. *s*, $NH_2$(Orn)); 7.82 (*d*, *J* = 8.2, NH(Val$_1$)); 7.47–7.14 (*m*, 5 H); 4.83 (*m*, $H_\alpha$(Orn$_{11}$)); 4.67 (*m*, $H_\alpha$(Orn$_4$), $H_\alpha$(Orn$_9$)); 4.64–4.48 (*m*, $H_\alpha$(D-Phe$_{13}$), $H_\alpha$(Orn$_2$), $H_\alpha$(Leu$_3$), $H_\alpha$(Leu$_8$), $H_\alpha$(Leu$_{12}$)); 4.42–4.33 (*m*, $H_\alpha$(Pro$_{14}$)); 4.29 (*t*, *J* = 7.7, $H_\alpha$(Val$_5$), $H_\alpha$(Val$_{10}$)); 4.20–4.11 (*m*, 1 H); 4.06 (*t*, *J* = 8.4, $H_\alpha$(Val$_1$)); 4.02 (*d*, *J* = 8.4, 1 H); 3.77–3.62 (*m*, 1 H); 3.60 (*s*, 1 H); 3.25–3.05 (*m*, 3 H); 3.02–2.85 (*m*, 8 H); 2.59 (*d*, *J* = 8.3, 1 H); 2.28–1.50 (*m*, 33 H); 1.40 (*q*, *J* = 6.2, 1 H); 1.09–0.76 (*m*, 36 H). $^{13}$C-NMR (151 MHz, $CD_3OH$): 175.5; 175.1; 174.6; 174.3; 174.1; 173.9; 173.7; 173.6; 173.5; 173.4; 173.3; 172.8; 137.2; 130.5; 129.8; 128.5; 89.2; 79.6; 74.3; 68.2; 62.0; 61.1; 60.2; 59.9; 55.8; 53.9; 53.8; 53.8; 53.3; 53.2; 53.0; 52.2; 49.7; 48.0; 43.7; 42.6; 42.3; 41.8; 40.8; 40.7; 40.6; 40.0; 37.6; 32.5; 31.8; 31.7; 31.0; 30.7; 30.1; 30.0; 26.2; 26.0; 25.9; 25.3; 25.1; 24.7; 23.9; 23.4; 23.0; 22.1; 20.0; 20.0; 20.0; 19.6; 18.7; 18.6. HR-ESI-MS: 1480.7266 ($[M+H]^+$, $C_{73}H_{126}N_{17}O_{15}^+$; calc. 1480.9614).

*cyclo[(3-OBn)SAA$_5$-Leu-Orn-Val-Orn-Leu-$^D$Phe-Pro-Val-Orn-Leu-$^D$Orn-Val] TFA Salt* (= *3-[(3S,6S,9S,12S,15S,19R,20R,22R,25S,28S,31S,40R,45aS)-6,28,34-Tris(3-aminopropyl)-40-benzyl-20-(benzyloxy)tetratetracontahydro-9,25,37-tris(2-methylpropyl)-1,4,7,10,13,16,23,26,29,32,35,38,41-tridecaoxo-3,15,31-tri(propan-2-yl)-1*H*-19,22-epoxypyrrolo[2,1-r][1,4,7,10,13,16,19,22,25,28,31,34,37]tridecaazacyclotritetracontin-12-yl]propan-1-aminium Trifluoroacetate*; **12**). SAA **16b** (33.2 mg, 1.2 equiv.) was pre-activated with HCTU (1.2 equiv., 50 mg) and Et$N^iPr_2$ (3 equiv., 60 µl) in 10 ml of NMP, and subsequently coupled to the L-O-V-$^D$O-L resin (200 mg, 0.1 mmol, 0.5 mmol/g) for 4 h (mini-cleavage: LC/MS: $t_R$ 6.31 min, linear gradient 10 → 90% *B* in 13.5 min; *m/z* 831.53 ($[M+H]^+$)). The resin (0.05 mmol) was subjected to steps *c*–*g*, and the Boc-deprotected peptide was purified by RP-HPLC (linear gradient of 36–45%, 3 CV) to give **12** (10.2 mg, 5.03 µmol, 10%). White amorphous powder. LC/MS: $t_R$ 5.64 min, linear gradient 10 → 90% *B* in 13.5 min; *m/z* 1572.4 ($[M+H]^+$). $^1$H-NMR (600 MHz, $CD_3OH$): 8.84 (*s*, NH(D-Phe$_{13}$)); 8.55 (*d*, *J* = 7.8, NH(Orn$_9$)); 8.53 (*d*, *J* = 8.1, NH(Orn$_2$)); 8.48 (*d*, *J* = 7.7, NH(Orn$_{11}$)); 8.46 (*d*, *J* = 9.7, NH(Leu$_{12}$)); 8.43 (*t*, *J* = 5.7, NH(SAA)); 8.35 (*d*, *J* = 8.2, NH(Leu$_3$)); 8.20 (*d*, *J* = 8.0, NH(Val$_5$)); 8.18 (*d*, *J* = 8.3, NH(Leu$_8$)); 8.14 (*d*, *J* = 7.8, NH(Orn$_4$)); 8.09 (*d*, *J* = 8.5, NH(Val$_{10}$)); 7.87 (br. *s*, $NH_2$(Orn)); 7.82 (*d*, *J* = 8.2, NH(Val$_1$)); 7.52–7.12 (*m*, 10 H); 4.86–4.83 (*m*, $H_\alpha$(Orn$_{11}$); 4.74–4.65 (*m*, $H_\alpha$(Orn$_4$), $H_\alpha$(Orn$_9$)); 4.64–4.48 (*m*, $H_\alpha$(Orn$_2$), $H_\alpha$(Leu$_3$), $H_\alpha$(Leu$_8$), $H_\alpha$(Leu$_{12}$), $H_\alpha$(D-Phe$_{13}$)); 4.40–4.34 (*m*, $H_\alpha$(Pro$_{13}$)); 4.32–4.29 (*m*, $H_\alpha$(Val$_5$), $H_\alpha$(Val$_{10}$)); 4.24–4.17 (*m*, 1 H); 4.06 (*t*, *J* = 8.4, $H_\alpha$(Val$_1$)); 3.99 (*d*, *J* = 4.8, 1 H); 3.75–3.62 (*m*, 2 H); 3.35 (*s*, 3 H); 3.13–3.05 (*m*, 3 H); 2.98–2.95 (*m*, 8 H); 2.65–2.58 (*m*, 1 H); 2.45 (*dd*, *J* = 12.7, 6.8, 1 H); 2.26 (*dd*, *J* = 15.1, 6.8, 1 H); 2.12 (*dd*, *J* = 13.4, 6.7, 1 H); 2.08–1.49 (*m*, 29 H); 1.45–1.33 (*m*, 1 H); 1.21 (*s*, 1 H); 1.07–0.75 (*m*, 36 H). $^{13}$C-NMR (151 MHz, $CD_3OH$): 175.2; 175.0; 174.6; 174.2; 174.1; 173.9; 173.7; 173.5; 173.4; 173.4; 173.3; 172.8; 163.0; 162.8; 139.3; 137.2; 130.5; 129.8; 129.5; 128.9; 128.9; 128.5; 86.9; 82.0; 79.8; 72.2; 62.0; 61.1; 60.2; 59.9; 55.8; 53.9; 53.8; 53.3; 53.2; 53.1; 52.2; 50.0; 49.7; 48.0; 43.7; 42.6; 42.3; 41.8; 40.8; 40.7; 40.6; 37.6; 37.1; 32.6; 31.8; 31.7; 31.2; 31.0; 30.9; 30.7; 30.1; 30.0; 26.2; 26.0; 25.9; 25.3; 25.1; 24.7; 23.9; 23.4;

23.1; 23.0; 22.1; 22.1; 20.0; 20.0; 19.6; 18.7; 18.5. HR-ESI-MS: 1571.0091 ($[M+H]^+$, $C_{80}H_{132}N_{17}O_{15}^+$; calc. 1571.0083).

*cyclo[(3-OH)SAA$_6$-Leu-Orn-Val-Orn-Leu-$^D$Phe-Pro-Val-Orn-Leu-$^D$Orn-Val] TFA Salt* (= *3-[(3S,6S,9S,12S,15S,19R,20R,23R,26S,29S,32S,41R,46aS)-6,29,35-Tris(3-aminopropyl)-41-benzylhexatetracontahydro-20-hydroxy-9,26,38-tris(2-methylpropyl)-1,4,7,10,13,16,24,27,30,33,36,39,42-tridecaoxo-3,15,32-tri(propan-2-yl)-19,23-epoxypyrrolo[2,1-r][1,4,7,10,13,16,19,22,25,28,31,34,37]tridecaazacyclotetratetracontin-12-yl]propan-1-aminium Trifluoroacetate*; **13**). SAA **18a** (62.4 mg, 1.55 equiv.) was preactivated with HCTU (1.45 equiv., 120 mg) and $EtN^iPr_2$ (2.9 equiv., 96 µl) in 10 ml of NMP, and subsequently coupled to the L-O-V-$^D$O-L resin (400 mg, 0.2 mmol, 0.5 mmol/g) for 4 h (mini-cleavage: LC/MS: $t_R$ 5.28 min, linear gradient 10 → 90% *B* in 13.5 min; *m/z* 755.33 ($[M+H]^+$)). The resin (0.1 mmol) was subjected to steps *c*–*g*, and the Boc-deprotected peptide was purified by RP-HPLC (linear gradient of 31–40%, 3 CV) to give **13** (34.0 mg, 17.4 µmol, 17%). White amorphous powder. LC/MS: $t_R$ 5.09 min, linear gradient 10 → 90% *B* in 13.5 min; *m/z* 1496.2 ($[M+H]^+$). $^1$H-NMR (600 MHz, $CD_3OH$): 8.86 (*d*, *J* = 3.5, NH(D-Phe$_{13}$)); 8.66 (*d*, *J* = 8.5, NH(Orn$_9$)); 8.52 (*d*, *J* = 9.1, NH(Orn$_{11}$)); 8.51 (*d*, *J* = 9.4, NH(Leu$_{12}$)); 8.46 (*d*, *J* = 8.7, NH(Orn$_4$)); 8.44 (*d*, *J* = 8.7, NH(Leu$_3$)); 8.43 (*d*, *J* = 8.7, NH(Orn$_2$)); 8.38 (*d*, *J* = 8.9, NH(Val$_{10}$)); 8.32–8.23 (*m*, (NH(SAA)); 8.14 (*d*, *J* = 8.6, NH(Val$_5$)); 7.88 (br. *s*, $NH_2$(Orn)); 7.78 (*d*, *J* = 8.4, NH(Val$_1$)); 7.67 (*d*, *J* = 6.7, NH(Leu$_8$)); 7.37–7.20 (*m*, 5 H); 5.05–5.03 (*m*, $H_\alpha$(Orn$_4$)); 5.01–4.98 (*m*, $H_\alpha$(Orn$_9$)); 4.90–4.88 (*m*, $H_\alpha$(Orn$_2$), $H_\alpha$(Orn$_{11}$)); 4.68–4.66 (*m*, $H_\alpha$(Leu$_3$)); 4.58–4.56 (*m*, $H_\alpha$(Leu$_{12}$), $H_\alpha$(D-Phe$_{13}$)); 4.51–4.42 (*m*, $H_\alpha$(Val$_5$), $H_\alpha$(Leu$_8$)); 4.40–4.38 (*m*, $H_\alpha$(Pro$_{14}$), $H_\alpha$(Val$_{10}$)); 4.16 (*t*, *J* = 8.1, $H_\alpha$(Val$_1$)); 3.88–3.80 (*m*, 1 H); 3.72–3.69 (*m*, 1 H); 3.65 (*s*, 1 H); 3.61–3.56 (*m*, 1 H); 3.51–3.37 (*m*, 1 H); 3.26–3.16 (*m*, 2 H); 3.12–2.82 (*m*, 10 H); 2.60 (*dd*, *J* = 16.9, 8.7, 1 H); 2.37–2.17 (*m*, 2 H); 2.17–1.42 (*m*, 33 H); 1.45–1.30 (*m*, 1 H); 1.10–0.71 (*m*, 36 H). $^{13}$C-NMR (151 MHz, $CD_3OH$): 174.6; 174.3; 174.0; 173.8; 173.6; 173.5; 173.3; 173.2; 173.0; 172.9; 163.2; 137.2; 130.5; 129.8; 128.6; 83.9; 77.2; 68.2; 62.0; 60.7; 59.2; 55.8; 54.1; 53.9; 53.5; 53.2; 53.1; 52.8; 52.3; 49.7; 48.0; 43.8; 42.4; 42.3; 42.0; 40.7; 37.7; 33.4; 33.0; 32.6; 32.2; 32.0; 30.7; 28.9; 26.3; 26.0; 25.8; 25.1; 24.8; 24.7; 24.5; 24.2; 23.1; 23.1; 23.0; 22.3; 20.3; 20.1; 19.8; 19.4; 18.7; 18.0. HR-ESI-MS: 1494.9780 ($[M+H]^+$, $C_{74}H_{128}N_{17}O_{15}^+$; calc. 1494.9770).

*cyclo[(3-OBn)SAA$_6$-Leu-Orn-Val-Orn-Leu-$^D$Phe-Pro-Val-Orn-Leu-$^D$Orn-Val] TFA Salt* (= *3-[(3S,6S,9S,12S,15S,19R,20R,23R,26S,29S,32S,41R,46aS)-6,29,35-Tris(3-aminopropyl)-41-benzyl-20-(benzyloxy)hexatetracontahydro-9,26,38-tris(2-methylpropyl)-1,4,7,10,13,16,24,27,30,33,36,39,42-tridecaoxo-3,15,32-tri(propan-2-yl)-19,23-epoxypyrrolo[2,1-r][1,4,7,10,13,16,19,22,25,28,31,34,37]tridecaazacyclotetratetracontin-12-yl]propan-1-aminium Trifluoroacetate*; **14**). SAA **18b** (58 mg, 2 equiv.) was preactivated with HCTU (2 equiv., 83 mg) and $EtN^iPr_2$ (4 equiv., 66 µl) in 10 ml of NMP, and subsequently coupled to the L-O-V-$^D$O-L resin (200 mg, 0.1 mmol, 0.5 mmol/g) for 4 h (mini-cleavage: LC/MS: $t_R$ 6.68 min, linear gradient 10 → 90% *B* in 13.5 min; *m/z* 845.33 ($[M+H]^+$)). The resin (0.1 mmol) was subjected to steps *c*–*g*, and Boc-deprotected peptide was purified by RP-HPLC (linear gradient of 31–40%, 3 CV) to give **14** (53.56 mg, 26.2 µmol, 26%). White amorphous powder. LC/MS: $t_R$ 5.25 min, linear gradient 10 → 90% *B* in 13.5 min; *m/z* 1585.4 ($[M+H]^+$). $^1$H-NMR (750 MHz, $CD_3OH$): 8.87 (*d*, *J* = 3.6, NH(D-Phe$_{13}$)); 8.67 (*d*, *J* = 8.5, NH(Orn$_9$)); 8.52 (*d*, *J* = 7.4, NH(Orn$_{11}$), NH(Leu$_{12}$)); 8.45 (*d*, *J* = 6.1, NH(Orn$_4$)); 8.44 (*d*, *J* = 8.5, NH(Leu$_3$), NH(Orn$_2$)); 8.37 (*d*, *J* = 8.0, NH(Val$_{10}$)); 8.27–8.20 (*m*, NH(SAA)); 8.16 (*d*, *J* = 8.7, NH(Val$_5$)); 7.90 (br. *s*, $NH_2$(Orn)); 7.77 (*d*, *J* = 8.4, NH(Val$_1$)); 7.69 (*d*, *J* = 6.4, NH(Leu$_8$)); 7.36–7.21 (*m*, 10 H); 5.06–5.03 (*m*, $H_\alpha$(Orn$_4$)); 5.00–4.98 (*m*, $H_\alpha$(Orn$_9$)); 4.91–4.89 (*m*, $H_\alpha$(Orn$_2$), $H_\alpha$(Orn$_{11}$)); 4.67–4.65 (*m*, $H_\alpha$(Leu$_3$)); 4.65 (*d*, *J* = 11.4, 1 H); 4.60–4.58 (*m*, $H_\alpha$(Leu$_{12}$), $H_\alpha$(D-Phe$_{13}$)); 4.57–4.51 (*m*, $H_\alpha$(D-Phe$_{13}$)); 4.46–4.43 (*m*, $H_\alpha$(Val$_5$)); 4.45 (*d*, *J* = 11.4, 1 H); 4.43–4.36 (*m*, $H_\alpha$(Leu$_8$), $H_\alpha$(Pro$_{14}$)); 4.17 (*t*, *J* = 8.2, $H_\alpha$(Val$_1$)); 3.91–3.86 (*m*, 1 H); 3.72–3.69 (*m*, 1 H); 3.65 (*s*, 1 H); 3.64–3.55 (*m*, 1 H); 3.44–3.42 (*m*, 1 H); 3.40–3.34 (*m*, 1 H); 3.28–3.26 (*m*, 1 H); 3.07 (*dd*, *J* = 12.7, 5.4, 1 H); 3.02 (*s*, 1 H); 2.98–2.88 (*m*, 7 H); 2.83 (br. *s*, 1 H); 2.59–2.57 (*m*, 1 H); 2.43–2.41 (*m*, 1 H); 2.32–2.22 (*m*, 1 H); 2.12–2.09 (*m*, 1 H); 2.06–1.86 (*m*, 5 H); 1.82–1.46 (*m*, 25 H); 1.40–1.33 (*m*, 1 H); 1.00–0.88 (*m*, 36 H). $^{13}$C-NMR (189 MHz, $CD_3OH$): 174.6; 174.2; 174.0; 173.8; 173.6; 173.5; 173.2; 173.2; 173.0; 172.9; 163.1; 162.9; 139.7; 137.2; 130.5; 129.8; 129.4; 129.0; 128.9; 128.5; 82.1; 77.3; 75.5; 71.8; 62.0; 60.8; 59.4; 59.3; 55.8; 54.2; 53.9; 53.6; 53.3; 53.1; 52.9; 52.3; 48.0; 43.8; 42.3; 42.3; 42.0; 40.8; 37.6; 33.3; 32.6; 32.0; 30.7; 29.4; 28.5; 26.3; 26.0; 25.8; 25.1; 24.8; 24.7; 24.5; 24.1; 23.1; 23.1; 23.0; 23.0; 22.3; 20.3; 20.1; 19.8; 19.4; 18.7; 18.0. HR-ESI-MS: 1585.0253 ($[M+H]^+$, $C_{81}H_{134}N_{17}O_{15}^+$; calc. 1585.0240).

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*Received August 28, 2012*