The Structure of Hormaomycin and One of Its All-Peptide Aza-Analogues in Solution: Syntheses and Biological Activities of New Hormaomycin Analogues

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Abstract: Four new aza-analogues of hormaomycin **1**, a secondary metabolite with interesting biological activities produced by *Streptomyces griseoflavus*, were synthesized and subjected to preliminary tests of their antibiotic activity to provide new insights into the structure–activity relationship studies of this class of compounds. The solution structures of hormaomycin **1** and its aza-analogue **2a** were determined by NMR spectroscopy. The data exhibited a reasonably rigid conformation for both molecules, stabilized by stacking interactions between the aromatic moieties attached to the ring and the side chain. According to NMR-spectral data the aza-analogue *epi*-**2a** has a rather different conformation and indeed shows no antibacterial activity whatsoever.

Keywords: amino acids · NMR spectroscopy · peptides · structure elucidation · synthetic methods

Introduction

Hormaomycin **1** is a secondary metabolite produced by *Streptomyces griseoflavus* (strain W-384).[1,2] This peptide lactone contains (*S*)-isoleucine [(*S*)-Ile] as the only proteinogenic amino acid along with two units of (2*S*,3*R*)-3-methylphenylalanine [(βMe)Phe], one of (*R*)-*allo*-threonine [*a*-Thr] as well as two moieties of (1′*R*,2′*R*)-3-(2′-nitrocyclopropyl)alanine [(3-Ncp)Ala; the (2*S*)-diastereomer in the side chain and the (2*R*)-diastereomer in the ring part of the molecule] as well as one residue of (2*S*,4*R*)-4-(*Z*)-propenylproline [(4-Pe)Pro] (Figure 1). The side chain of **1** is terminated by an amide-bound 5-chloro-1-hydroxypyrrole-2-carboxylic acid [Chpca]. The latter three constituents have never been found in any natural product before. Besides challenging structural features, hormaomycin **1** possesses quite an interesting spectrum of biological activities, including a marked influence on the secondary metabolite production of other streptomycetes, an exceptionally selective antibiotic activity against coryneform bacteria,[1] and also an antimalaria activity.[3]

The unique biological properties of **1** prompted feeding experiments with amino acids, which possibly could replace (3-Ncp)Ala. This approach yielded several new analogues of hormaomycin,[4] however, the precursor-directed biosynthesis is apparently limited to such modifications of the building blocks, which are tolerated by the hormaomycin synthetase. Thus, it was for example impossible to isolate analogues of hormaomycin with a substituted or modified *allo*-threonine (*a*-Thr) moiety.[5] On the other hand, it appeared to be interesting to study the biological and, in this context, the conformational properties of hormaomycin and especially its cyclopeptide analogue **2a** with (2*R*,3*R*)-diaminobutyric acid instead of (*R*)-*allo*-threonine in the macrocycle. The more rigid additional amide bond might have a significant influence on the intramolecular hydrogen bonds and thereby on the global structure in solution as compared to that of the peptide lactone. This comparison might provide insights into the structural requirements for biological activities of hormaomycin **1** itself and of hormaomycin analogues. Since

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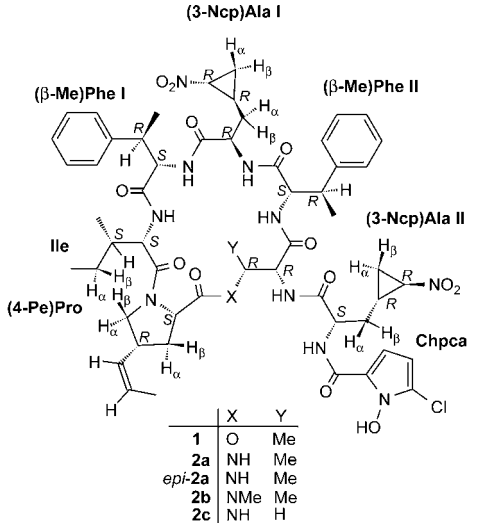


	X	Y
1	O	Me
2a	NH	Me
epi-**2a**	NH	Me
2b	NMe	Me
2c	NH	H

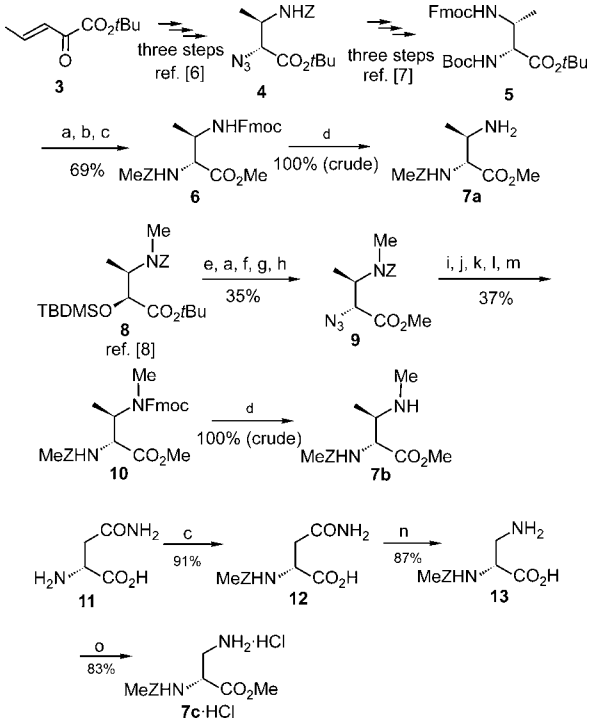
Figure 1. Structural formulas of hormaomycin **1** and its aza-analogues **2a–c** and *epi*-**2a**. Analogue *epi*-**2a** contains an (*R*)-*a*-Ile instead of an Ile moiety.

amide bonds are usually much more stable towards enzymatic cleavage than ester linkages, aza-analogues ought to have longer half-lives in vivo and thereby provide prolonged biological activity. Herewith we present the first chemical syntheses of the hormaomycin analogues **2a–c** and *epi*-**2a** as well as a preliminary evaluation of their biological activities along with a thorough investigation of the three-dimensional structure of hormaomycin **1** and its aza-analogue **2a** in solution by a combination of modern NMR spectroscopic techniques.

Results and Discussion

Synthesis of hormaomycin analogues: At the outset, the appropriate N_α-*p*-methylbenzyloxycarbonyl (MeZ) protected diamino acid methyl esters **7a–c** were synthesized (Scheme 1). The α-azido *tert*-butyl ester **4**, which was prepared according to a published procedure[6] with a Sharpless asymmetric aminohydroxylation as a key step followed by stereoselective azidation, was transformed into the fully protected (2*R*,3*R*)-2,3-diaminobutyric acid (*a*-Dab) derivative **5** as described by Wen et al.[7] The free acid, after simultaneous removal of the *N*-Boc and *O*-*tert*-butyl groups from **5** with trifluoroacetic acid, was esterified with methanol, and the resulting N_β-protected diamino acid methyl ester was acetylated with MeZOSu to give **6** in 69% yield over three steps. Removal of the *N*-Fmoc group just before the next step gave the methyl ester **7a**.

The fully protected diamino acid **10** was synthesized starting from the known *tert*-butyl ester **8**.[8] After removal of the *tert*-butyldimethylsilyl group followed by cleavage of the *tert*-butyl ester, the appropriate *N*-Z-protected isothreonine was esterified with diazomethane to give an intermediate, which was further converted to the corresponding mesylate.



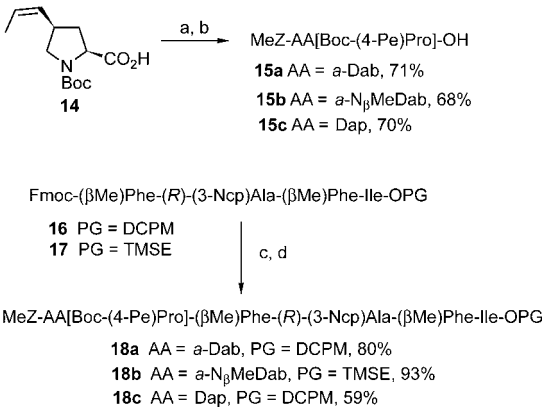
Scheme 1. Syntheses of the suitably protected diamino acids **7a–c**. a) TFA, 20°C, 1 h. b) $SOCl_2$, MeOH, −20 → 50°C, 21 h. c) MeZOSu, $NaHCO_3$, acetone, H_2O, 20°C, 1.5 h. d) 50% Et_2NH in MeCN, 20°C, 40 min. e) 5% aq. HF, MeCN, 0 → 20°C, 4 h. f) CH_2N_2, Et_2O/MeOH, 20°C, 30 min. g) MsCl, Et_3N, CH_2Cl_2, −30 → 20°C, 5 h. h) NaN_3, DMF, 75°C, 15 h. i) Ph_3P, THF/H_2O, 20°C, 24 h, then Boc_2O, 20°C, 24 h. j) H_2, 10% Pd/C, EtOAc, 20°C, 3 h. k) FmocOPfp, HOAt (cat.), TMP, EtOAc, 20°C, 15 h. l) 2M HCl, EtOAc, 20°C, 3 h. m) MeZOSu, DIEA, TMP, MeCN, 20°C, 16 h. n) Iodobenzene bis(trifluoroacetate), pyridine, DMF/H_2O, 20°C, 5 h. o) $SOCl_2$, MeOH, −20 → 20°C, 24 h. MeZOSu = *p*-methylbenzyl-*N*-hydroxysuccinyl carbonate, FmocOPfp = (9-fluorenyl)methyl-pentafluorophenyl carbonate; HOAt = 7-aza-1-hydroxybenzotriazole, TMP = 2,4,6-trimethylpyridine, DIEA = *N*,*N*-diisopropylethylamine, Fmoc = (9-fluorenyl)methyloxycarbonyl, MeZ = *p*-methylbenzyloxycarbonyl, TBDMS = *tert*-butyldimethylsilyl.

This transformation was followed by displacement of the mesylate by an azide group with NaN_3 in DMF to give the azido ester **9**, which was further transformed into the N_α-Boc, N_β-Z protected (2*R*,3*R*)-3-amino-2-methylaminobutyric (*a*-N_βMeDab) acid methyl ester, by treatment first with triphenylphosphine and water, and then with Boc_2O. Subsequent removal of the Z group by hydrogenolysis was followed by introduction of the Fmoc group to give the intermediate N_α-Boc, N_β-Fmoc protected *a*-N_βMeDab methyl ester, which, after removal of the Boc group, was finally acylated with MeZOSu to give **10** in 13% yield over ten steps. The *N*-Fmoc group in **10** was then removed to give **7b**. The latter was immediately used in the peptide coupling step.

The N_α-MeZ protected 2,3-diaminopropionic acid ester **7c** was obtained as a hydrochloride by esterification with methanol of the intermediate **13**, which in turn was prepared in 76% yield over three steps starting from (*R*)-asparagine (**11**) by initial acylation with MeZOSu and subsequent oxi-

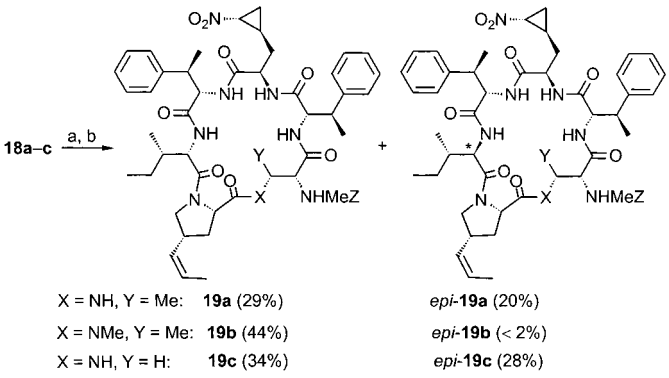
dation with iodobenzene bis(trifluoroacetate) in close analogy to a published procedure.[9]

The diamino esters **7a–c** were coupled with the *N*-Boc-protected (2*S*,3*R*)-4-(*Z*)-propenylproline **14**[10] to give the intermediate methyl esters (Scheme 2).[11] Treatment of the latter with tetrabutylammonium hydroxide[12] gave the peptide acids **15a–c** in 71, 68 and 70% yield over two steps, respectively, which were coupled with the *O*-dicyclopropylmethyl (DCPM) protected tetrapeptide **16**[2a] (**15a** and **c**) or with the *O*-(2-trimethylsilyl)ethyl (TMSE) protected tetrapeptide **17**[13] (**15b**), after deprotection of their terminal amino groups, to yield the branched hexapeptides **18a** (80%), **18b** (93%), and **18c** (59%), respectively.



Scheme 2. Syntheses of the linear peptide precursors **18a–c**. a) **7a–c**, EDC, HOAt, TMP, CH_2Cl_2, 0 → 20°C, 16 h. b) 40% aq. $Bu_4N^+OH^-$, THF, 0°C, 45 min. c) 50% Et_2NH in THF, 20°C, 40 min. d) **15a–c**, HATU, HOAt, TMP, CH_2Cl_2, 0 → 20°C, 15 h. EDC = *N*′-(3-dimethylaminopropyl)-*N*-ethylcarbodiimide hydrochloride, HATU = *O*-(7-azabenzotriazole-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate, DCPM = dicyclopropylmethyl, TMSE = 2-trimethylsilyl)ethyl, Dap = 2,3-diaminopropionic acid.

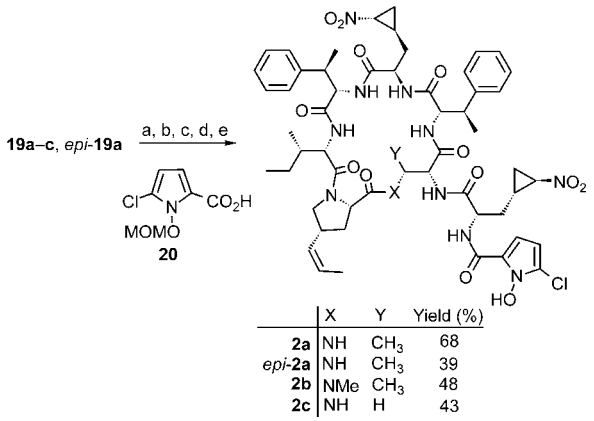
The acidolytic removal of the Boc and DCPM groups from the termini of **18a** and **18c**, as well as the sequential removal first of the TMSE group with tetrabutylammonium fluoride, and then the Boc group with acid from the terminus of **18b** occurred almost quantitatively, and was succeeded by macrocyclization, by using *O*-(7-azabenzotriazole-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HATU)[14] in the presence of 7-aza-1-hydroxybenzotriazole (HOAt)[14] under high-dilution conditions (Scheme 3). The cyclization of the hexapeptides, containing *a*-Dab or Dap residues, caused significant epimerization at the α-carbon of the Ile residue (Ile → (*R*)-*a*-Ile)[15] and gave, after HPLC separation, the epimeric macrocycles, **19a** (28%) and *epi*-**19a** (19%), as well as **19c** (34%) and *epi*-**19c** (25%), respectively. In contrast, the cyclization of the *a*-N_βMeDab-containing peptide (similar to the synthesis of the *N*-MeZ protected ring part of hormaomycin **1**)[2a] gave almost exclusively the cyclic peptide **19b** (44%) along with only traces (<2%) of the epimer. Not surprisingly, the epimeric products exhibited features in their ^1H and ^{13}C NMR spectra (chemical shifts, coupling constants and line shapes) as well



Scheme 3. Cyclization of the linear precursors **18a–c**. a) 2 M HCl, EtOAc, 20°C, 1 h (for **18a** and **18c**) or $Bu_4N^+F^-$, THF, 20 → 55°C, 2 h then 2 M HCl, in EtOAc, 20°C, 1 h (for **18b**). b) HATU, DIEA, TMP, CH_2Cl_2, 0.1 mM, 0 → 20°C, 18–22 h.

as optical rotation values quite different from those of **19a** and **19c** indicating distinctions in their solution structures.

The *N*-MeZ protected cyclohexapeptides were subsequently first deprotected and then coupled with *N*-Teoc-protected (2*S*,1′*R*,2′*R*)-(3-Ncp)Ala-OH[2a] (Scheme 4). Removal of the Teoc group and coupling of the intermediates with *O*-MOM protected Chpca-OH **20**[2a,10] gave the *O*-MOM protected hormaomycin aza-analogues. Finally, removal of the MOM group gave the target compounds **2a–c** and *epi*-**2a**.



	X	Y	Yield (%)
2a	NH	CH_3	68
epi-**2a**	NH	CH_3	39
2b	NMe	CH_3	48
2c	NH	H	43

Scheme 4. The final steps in the preparation of aza-analogues **2a–c** and *epi*-**2a**. a) Anisole, TFA, 20°C, 2 h. b) Teoc-(2*S*,1′*R*,2′*R*)-(3-Ncp)AlaOH, HATU, HOAt, DIEA, TMP, CH_2Cl_2, 20°C, 15 h. c) TFA, 20°C, 1 h. d) **20**, HATU, HOAt, DIEA, TMP, CH_2Cl_2, 20°C, 4 h. e) $MgBr_2 \cdot Et_2O$, EtSH, CH_2Cl_2, 20°C, 3–4 h. Teoc = (2-trimethylsilylethyl)oxycarbonyl. Analogue *epi*-**2a** contains an (*R*)-*a*-Ile instead of an Ile moiety.

NMR analysis and conformational modelling of hormaomycin 1 and its all-peptide aza-analogue 2a: The conformational analysis of hormaomycin **1** was performed in $CDCl_3$ solution at 293 K. Spin systems were identified by DQF-COSY, TOCSY and ^{13}C-, ^1H-HMBC experiments. Especially useful for the assignment of the aromatic components were the long-range cross peaks between the H_β and the C_{ipso} as

well as the $H_{aromatic}$ and C_β, because they provided the correct assignment of the two phenyl rings of (βMe)Phe I and II.[13,16]

The χ_1 angles of each component were determined by the combined use of coupling constants from P.E. COSY and ^{13}C-HMBC experiments and distance information from ROESY experiments. A two proton example is the χ_1 dihedral angle of *allo*-(*R*)-threonine. In the HMBC spectrum, a strong $^3J_{CH}$ correlation from CO ($\delta = 169.2$ ppm) to the β proton ($\delta = 5.44$ ppm) is visible. This together with a $^3J(H_\alpha,H_\beta)$ value of 5 Hz is consistent with a g$^-$ arrangement of the two protons.

The chemical shift values of the components are shown in Table 1 of the Supporting Information. One-dimensional proton spectra showed one predominant resonance for each amide NH, suggesting either one dominant isomer or fast conformational averaging on the NMR time scale in $CDCl_3$. The coexistence of slowly interconverting conformers could be ruled out by the absence of exchange cross peaks in the ROESY spectra and the correct number of resonances in the 1D-proton spectrum.

The enantiotopic H_β protons of (3-Ncp)Ala I exhibited $\Delta\delta$ values >1.5 ppm indicating a well defined structure. This agrees with the large chemical shift dispersion within the set of NH (6.54–9.13 ppm) and H_α (3.51–5.16 ppm) proton signals. Especially the long-range ROE values between the aromatic protons of Chpca and (βMe)Phe I indicate a compact conformation.[13]

The presence of strong $H_\alpha(i)$–NH(i+1) ROE values and the absence of $H_\alpha(i)$–$H_\alpha(i+1)$ cross peaks confirmed that all the amide bonds are in the *s-trans* conformation.

An *s-trans* conformation with respect to the Ile–Pro peptide bond was assigned according to characteristic ROE cross peaks between the H_α (Ile) and the H_δ [(4-Pe)Pro] as well as the absence of cross peaks between H_α (Ile) and H_α [(4-Pe)Pro]. Additionally, the differences in ^{13}C NMR chemical shifts of C_β–$C_\gamma = -1.7$ ppm [(4-Pe)Pro], are indicative of *trans*-peptide bonds.[17] The difference, directly related to the dihedral angle ψ(Pro), is usually in the range of 2–10 ppm for *cis*-Pro and 0–5 ppm in *trans*-Pro. In (4-Pe)Pro residue of hormaomycin **1**, the (4*R*)-substituent further increases the C_γ chemical shift value.

Cyclic hexapeptides normally adopt an all-*trans*-conformation about the peptide bonds and prefer a conformation with two β turns.[18] The hypothesis that the number of amino acids in cyclopeptides influences the type of secondary structure adopted was later proved in a modified version.[19] However, major influences by the side chains, especially of non-typical amino acids, have not been taken into account. This made predictions of the solution structure of hormaomycin **1** difficult. In fact, hormaomycin **1** combines a cyclic portion with an extended side chain consisting of two components. In addition, the ring contains one ester linkage.

From the restrained MD simulations and energy minimizations, one family of low-energy structures was generated, satisfying the ROE-derived restraints and dihedral angles (Figure 2). No ROE violation greater than 0.5 Å was observed. Further details about the calculation and NMR input data are to be found in the Experimental Section.

The average root mean square deviation (RMSD) of the backbone atoms compared to the average structure was 0.39 Å and for all heavy atoms 0.71 Å.

The propenyl substituent of the (4-Pe)Pro unit of hormaomycin **1** is found antiperiplanar relative to the pyrrolidine nitrogen. It adopts an equatorial position (Figure 2). Allylic 1,3-strain directs the *cis*-propenyl side chain of (4-Pe)Pro into one plane with the γ-hydrogen of the pyrrolidine ring.

The observation of both NH(i)–NH(i+1) and $H_\alpha(i)$–NH(i+1) ROE values indicates that the peptolide backbone exists in a tight turn. A strong ROE between H_α [(βMe)Phe II] and NH [(3-Ncp)Ala I] together with a weak cross peak between H_α [(3-Ncp)Ala I] and NH [(βMe)Phe I] indicate a β turn [(βMe)Phe II, (3-Ncp)Ala I, (βMe)Phe I, Ile]. The CD curves with a positive maximum at 213 nm and a negative maximum around 240 nm already indicated the presence of a β turn.[2b]

The general criterium for the presence of a β turn is that the distance between $C_\alpha(i)$ and $C_\alpha(i+3)$ is less than 7 Å. Type II and type II′ β turns are further differentiated by their dihedral angles of the residues i+1 and i+2 (Table 1). The presence of a CO(i)–HN(i+3) hydrogen bond is possible, but not necessary for a stabilization of the β turn. The structure of hormaomycin **1** exhibits a $C_\alpha(i)$–$C_\alpha(i+3)$ distance of 7 Å for the components Ile and (βMe)Phe II. These two constitute the i and i+3 position (i+3 and i position) of two β turns in the structure of **1**. A γ turn can be excluded because the distances between H_α [(βMe)Phe II]–H_α [(βMe)Phe I] of 6.9 Å and H_α(Ile)–H_β(*a*-Thr) of 6.8 Å are too long.

A type II′ (inverse II) turn is formed with (βMe)Phe II at position i and with (3-Ncp)Ala I and (βMe)Phe I as the central residues (i+1) and (i+2), respectively. The presence of a $H_\alpha(i+1)$–HN(i+2) ROE and the absence of other HN–HN cross peaks differentiates this β turn from the other β turn of hormaomycin **1** which belongs to type II according to the corresponding dihedral angles (Table 1). The type II β turn is formed by Ile at the i position and (4-Pe)Pro and *a*-Thr as the central residues. Proline residues are typically found at the i+1 position of type I and type II β turns.

Table 1. Dihedral angles [°] of ideal β turns of type II and II′ and of the corner components of hormaomycin **1**.

	$\phi(i+1)$	$\psi(i+1)$	$\phi(i+2)$	$\psi(i+2)$
ideal type II	−60	+120	+80	0
ideal type II′	+60	−120	−80	0
(4-Pe)Pro, *a*-Thr	−61	+142	+90	−77
(3-Ncp)Ala I, (βMe)Phe I	+69	−134	−90	−47

Ideal β turns are ten-membered rings when the hydrogen bond is incorporated. In the case of hormaomycin **1**, the type II β turn is composed of (*R*)-*allo*-threonine at the ***i*+2** position and therefore contains the C_β as an additional atom.

Because of the unusual components and the overall structure that appears to be governed by long-range side-chain interactions, the β turns deviate from the ideal values. It is important to underline that the standard distances observed for turns in peptides and proteins containing only (*R*)- or (*S*)-residues cannot be used here.[20]

In general, distances in oligopeptides are strongly influenced by the configurations of the contained amino acids. (*S*)-Xaa-(*R*)-Yaa and (*R*)-Xaa-(*S*)-Yaa dyads have a high tendency to be in the corner positions of type II and type II′ turns, respectively. Indeed, the type II′ β turn in hormaomycin **1** is formed with the residue of (3-Ncp)Ala I [(*R*)-amino acid] in the corner position followed by (βMe)Phe I [(*S*)-amino acid].

With the oxygen of the ester linkage in **1** replaced by an NH in **2a**, the ϕ angle (+90°) of the *i*+2 residue (*a*-Thr) is almost identical with the ideal ϕ angle of a type II turn (+80°). The dihedral angle defined by O-C_α-C_β-CO (taken as $\psi(i+2)$) is substantially different from an ideal type II. It is therefore reasonable to refer to it as "type II-like". The dihedral angles at the *i*+1 position agree with the type II turn ($\phi=-61$ and $\psi=+142°$). The twisted nature of the β turns results in a figure-eight like overall structure for the macrocyclic ring (Figure 3).

Further corroboration of the structure is derived from the detailed analysis of the chemical shifts presented in the Experimental Section and Supporting Information.

The structure of a peptide is not only determined by the backbone conformation, but also the orientation of the side chains. Many conformational studies have shown that the rotamer distribution is the more shifted to a single rotamer, the more "rigid" the backbone is.[21] Hence, the side-chain conformation can be taken as an indicator for the rigidity of the molecule. The two aromatic rings of (βMe)Phe II and Chpca are stacked in-line with each other (Figure 2). The compact overall shape of hormaomycin **1** is dictated by these side-chain interactions which in turn allow only a rigid macrocyclic structure.

The assignments of proton and carbon resonances of the aza-analogue **2a** are compiled in Table 2 of the Supporting Information. Due to signal overlap two dihedral angles (H_α/$H_{3\beta}$ [(4-Pe)Pro] and H_γ/$H_{\delta\alpha}$ [(4-Pe)Pro] could not be determined. All the others, which have been determined for hormaomycin **1**, were also determined for **2a**. An identical range of values was obtained with only one differing dihedral angle in the side chain of isoleucin (C_α-C_β-C_γ-C_δ = +180° for **2a** and −60° for **1**). The side chain is therefore more directed to the solvent. The ROE values measured for **2a** differed only slightly, resulting in the same classification into strong, medium and weak as for hormaomycin **1**. An additional ROESY cross peak was observed between the HN attached to the C_β atom of the *a*-Dab unit and the protons of its methyl group.

The *s-trans*-conformation of all peptide bonds was confirmed by ROE cross peaks as established for hormaomycin **1**. Analogously, the ester linkage of *a*-Thr and (4-Pe)Pro in the calculated structure of hormaomycin **1** takes an *s-trans* orientation which is favored by the anomeric effect.

From the almost identical structural data obtained, one may conclude that the structure of the macrocyclic ring of the aza-analogue **2a** in solution does not differ from that of hormaomycin **1** (see Figure 4).

In general, cyclic peptides in which all the peptide bonds have *s-trans*-conformations lack internal motions in the backbone. This agrees with the present findings, that the modification in the macrocyclic ring from an ester to an amide linkage does not change the overall structure of the macrocycle. In the case of **2a**, the additional peptide bond also adopts an *s-trans*-conformation.

The investigation of the solution structure of the *N*-methyl-aza-analogue **2b** was considered to be useless because of an abundance of slowly equilibrating conformers. As the ^{1}H NMR spectrum of the *des*-methyl-aza-analogue **2c** is very similar to those of hormaomycin **1** and the aza-analogue **2a**, it is quite possible that this peptide in solution also adopts approximately the same overall conformation.

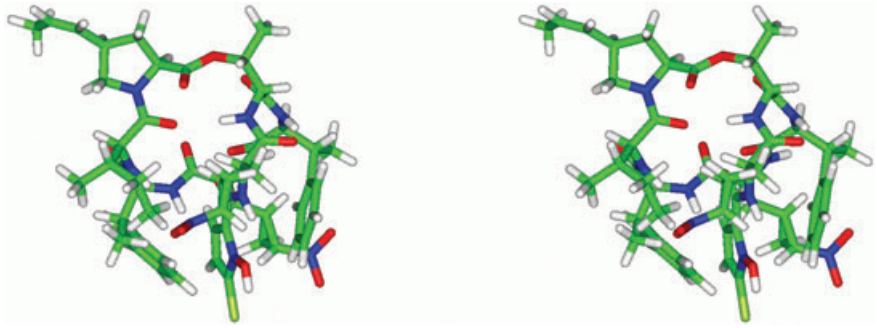


Figure 2. Stereoview of the average structure of hormaomycin **1** in $CDCl_3$.

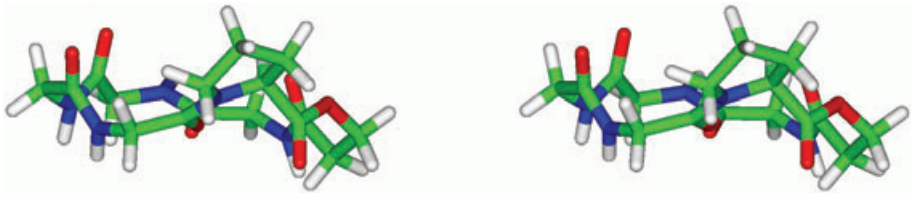


Figure 3. Stereoview of the macrocyclic ring of the average structure of hormaomycin **1** in $CDCl_3$.

Antibacterial activity: As an entry, the antibiotic activity of the new hormaomycin analogues against *Arthrobacter* species was tested (Tables 2, 3).[22]

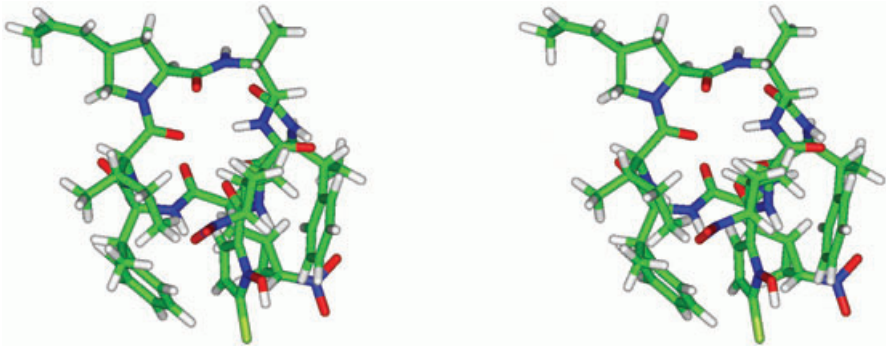


Figure 4. Average structure of the aza-analogous hormaomycin **2a**.

Table 2. Relative antibacterial activities of hormaomycin **1**, aza-analogues **2a** and *epi*-**2a** in serial dilution plate diffusion tests against *Arthrobacter crystallopoites* (strain 20117) (%) (estimated relative to the activity of hormaomycin at 5×10^{-2} mg per 9×0.5 mm plate) 28 °C.

Compound (mg pro plate)	5×10^{-2}	5×10^{-3}	5×10^{-4}	5×10^{-5}
hormaomycin **1**	100	94	71	39
2a	103	90	68	35
epi-**2a**	0	0	–	–

Table 3. Relative antibacterial activities of several compounds in serial dilution plate diffusion tests against *Arthrobacter oxidans* (strain 20119) (%) (estimated relative to the activity of hormaomycin at 1.5×10^{-2} mg per 6×0.65 mm plate) 28 °C.[23]

Compound (mg per plate)	1.5×10^{-2}	1.5×10^{-3}	1.5×10^{-4}
hormaomycin **1**	100	72	44
penicillin G	78	0	0
19a–c, *epi*-**19a**	0	–	–
epi-**19c**	22	0	0
2b	94	72	42
2c	94	83	58

Even these very preliminary biological tests give some information about structure–activity relationships for hormaomycin **1** and its analogues. At least the antibacterial activity of hormaomycin **1** can neither solely be attributed to its macrocyclic part nor to its side chain,[4b] but supposedly is associated with the whole molecule. The weak antibiotic activity of the cyclopeptide *epi*-**19c** may be due to a mode of action on bacteria which is different from that of hormaomycin **1**. The aza-analogues **2a–c** displayed spectral and solubility properties, as well as antibiotic activities very similar to those of the native compound **1**. In contrast, the *epi*-aza-analogue *epi*-**2a**, which exhibits CD and ^{1}H NMR spectra as well as solubility properties quite different from those of hormaomycin **1**, turned out to be totally inactive within the used test system.

Conclusion

We have synthesized several analogues of hormaomycin and investigated the structures of the title compound **1** and its aza-analogue **2a** by solution NMR experiments. The two structures turn out to be virtually identical. Consistent with this finding, **1** and **2a** exhibit similar antibiotic activities. The ^{1}H NMR spectra of *epi*-**2a** substantially differ from those of **1** and **2a** suggesting a different structure. Consistently, *epi*-**2a** is inactive in the antibiotic assay indicating that the conformation of the whole molecule is important for this biological activity.

Experimental Section

General remarks: Synthesis: ^{1}H NMR spectra: Bruker AM 250 (250 MHz), Varian Unity 300 (300 MHz), Varian Inova 600 (600 MHz). ^{1}H chemical shifts are reported in ppm relative to residual peaks of deuterated solvent or tetramethylsilane. Higher order NMR spectra were approximately interpreted as first-order spectra, if possible. The observed signal multiplicities are characterized as follows: s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, m = multiplet, as well as br = broad, Ar-H = aryl-H. ^{13}C NMR spectra [additional DEPT (Distortionless Enhancement by Polarization Transfer) or APT (Attached Proton Test)]: Bruker AM 250 (62.9 MHz), Varian Unity 300 (75.5 MHz) or Varian Inova 600 (125.7 MHz) instruments. ^{13}C chemical shifts are reported relative to peak of solvent or tetramethylsilane. The following abbreviations were applied: DEPT: + = primary or tertiary (positive signal in DEPT), − = secondary (negative signal in DEPT), C_{quat} = quaternary (no signal in DEPT); APT: + = primary or tertiary (positive signal in APT), − = secondary or quaternary (negative signal in APT); whenever it was necessary and possible HMBC (Heteronuclear Multiple Bond Connectivity) and/or HMQC (Heteronuclear Multiple Quantum Coherence) spectra were also measured. The signals marked with asterisk have been attributed with uncertain reliability. IR spectra: Bruker IFS 66 (FT-IR) spectrometer, samples measured as KBr pellets or oils between KBr plates. The IR spectra of all synthesized peptides showed a broad NH stretch band, arising from the amide moieties, between 3500 and 3250 cm^{-1}. MS: EI-MS: Finnigan MAT 95, 70 eV. High resolution EI-MS spectra with perfluorokerosene as reference substance; pre-selected ion peak matching at $R \geqslant 10000$ to be within ±2 ppm of the exact masses. ESI-MS: Finnigan LCQ. HPLC: pump: Kontron 322 system, detector: Kontron DAD 440, mixer: Kontron HPLC 360, data system: Kontron Kromasystem 200, columns: Knauer Nucleosil-100 C18 (analytical, 5 μm, 3 mm × 250 mm), preparative: A: Kromasil C18 (7 μm, 20 mm × 250 mm), B: Knauer Nucleosil-100 C18 (5 μm, 8 mm × 250 mm). Optical rotations: Perkin–Elmer 241 digital polarimeter, 1 dm cell; optical rotation values are given in 10^{-1} deg cm^2 g^{-1}; concentrations (c) are given in g per 100 mL. Circular dichroism: Jasco J 500 A. Molar ellipticities (Θ) are given in degree cm^2 10^{-1} mol^{-1}. M.p.: Büchi 510 capillary melting point apparatus, uncorrected values. TLC: Macherey–Nagel precoated sheets, 0.25 mm Sil G/UV$_{254}$. The chromatograms were viewed under UV light and/or by treatment with phosphomolybdic acid (10% in ethanol), or ninhydrin (0.2% in ethanol), or Ehrlich's reagent (freshly prepared solution of 1 g of 4-dimethylamino-benzaldehyde in 25 mL of 36% HCl and 75 mL methanol). Column chromatography: Merck silica gel, grade 60, 230–400 mesh and Baker silica gel, 40–140 mesh. Preparative TLC: Macherey–Nagel, silica gel SIL G/UV$_{254}$, layer thickness 0.25 mm (100 × 200 mm or 200 × 200 mm). Elemental analyses: Mikroanalytisches Laboratorium des Instituts für Organische und Biomolekulare Chemie der Universität Göttingen. Starting materials: Anhydrous solvents were pre-

pared according to standard methods by distillation over drying agents and were stored under argon. All other solvents were distilled before use. All reactions were carried out with magnetic stirring and, if air or moisture sensitive, in flame-dried glassware under argon or nitrogen. Organic extracts were dried with anhydrous $MgSO_4$. *tert*-Butyl (2*R*,3*R*)-2-azido-3-(benzyloxycarbonylamino)butyrate (**4**),[6] *tert*-butyl (2*R*,3*R*)-2-*tert*-butyloxycarbonylamino-3-(9-fluorenylmethyloxycarbonylamino)butyrate (**5**),[7] *tert*-butyl (2*S*,3*R*)-2-*tert*-butyldimethylsilyloxy-3-(benzyloxycarbonyl-*N*-methylamino)butyrate (**8**),[8] (2*S*,4*R*)-(N-*tert*-butyloxycarbonyl)-4-(*Z*)-propenylproline (**14**),[10] 1-hydroxy-7-aza-benzotriazole,[24] tetrapeptides **16**[2a] and **17**,[25] (2*S*,1′*S*,2′*R*)-[*N*-(2-trimethylsilyl)ethyloxycarbonyl]-(2′-nitrocyclopropyl)alanine,[2a] 5-chloro-1-methoxymethoxypyrrole-2-carboxylic acid (**20**)[10] were prepared as described elsewhere. Conformational analysis NMR studies: NMR spectra were recorded on Bruker DRX400 and DRX600 spectrometers. The concentration was 5 mM in $CDCl_3$ and measurements were run at 293 K. The assignments were carried out with the help of standard DQF-COSY (Double-Quantum Filtered Correlation Spectroscopy), TOCSY (Total Correlation Spectroscopy), ^{13}C-HSQC, ^{15}N-HSQC and ^{13}C-HMBC experiments. Typically 2 K data points in *F*2 and 512 experiments in *F*1 were acquired. In some cases, additional ROESY experiments were used to confirm the assignments made. The spectra were acquired with 16 transients and a relaxation delay of 2 s except the ROESY experiments with 80 transients. For ROESY experiments, a spinlock field of 3.1 kHz was used with a mixing time of 480 ms.[26] The TOCSY experiments were performed with a spinlock field of 6.25 kHz by using the MLEV17 sequence with mixing times of 40 and 80 ms. The data were zero filled and processed as a 4 K × 1 K matrix. P.E. COSY experiments were processed as an 8 K × 2 K matrix. To obtain the temperature coefficients of the amide proton chemical shifts, TOCSY spectra were recorded between +15 and +45 °C. To determine the χ_1 torsional angle constraints, the H_α–H_β coupling constants ($^3J_{\alpha\beta}$) from the 1D proton and P.E. COSY spectra, the intensity of the intraresidue ROEs (H_α–H_β, NH–H_β) and the intensity of the $^3J_{CH}$ HMBC cross peaks were used. Each amino acid residue was classified with respect to three rotamers, according to the patterns of the $^3J_{HH}$, $^3J_{CH}$ and ROE values. The stereospecific assignments were also established for the β-methylene protons. Assuming that the staggered rotamers are predominantly populated, qualitative considerations together with homonuclear coupling constants[13] are often sufficient for the assignment of diastereotopic methylene protons (Figure 1). The χ_1 angle was set at −60° when both the $^3J(H_\alpha$–$H_{\beta1})$ and the $^3J(H_\alpha$–$H_{\beta2})$ coupling constants are small. If one strong and one weak coupling is observed, χ_1 can be either 60 or 180°. To differentiate between these two cases, stereospecific assignments of the H_β protons are required. This was possible with the help of qualitative heteronuclear *J* couplings (between ^{13}CO and H_β) and ROE cross-peak intensities stemming from the different H_β protons. In this way a set of dihedral angles was obtained and this together with the ROE-derived distances was the input for a molecular modelling (MD) study.[13] *Molecular dynamics*: All molecular mechanics/dynamics simulations were performed with DISCOVER of Insight II (Accelrys) on a Silicon Graphics Octane workstation. The simulations were done using CVFF (Consistent Valence Force Field).[27] A distance-dependent dielectric constant ($\varepsilon = 4.8\,r$) was used. The molecular structure was first minimized. During a 100 ps MD run, 100 structures were sampled which represent starting conformations for the subsequent restrained MD. According to a simulated annealing approach, the resulting starting molecules were heated to 600 K initially, subsequently cooled and finally subjected to an energy minimization using both steepest descent and conjugate gradient methods successively.[28] The final structures were analyzed for similarities by comparing the RMSD deviations.

The distance and torsional angle constraints of Tables 3 and 4 in the Supporting Information were used as restraints in the MD runs as well as the final minimizations. Pseudo-atoms were used for the methyl protons and aromatic protons. Distance restraints derived from ROE-cross peaks, classified empirically as strong, medium and weak, were applied as biharmonic restraints with lower and upper boundaries of 2.0–2.8, 2.0–3.5, 2.0–5.0 Å, respectively. The configurations at the stereogenic carbon atoms were restrained.[13] Likewise, due to the detected *trans*-conformation of all peptide bonds, the ω dihedral angle was restrained to 180°.

Structural validation: The following four interresidual ROEs have not been used in the calculations for cross validation purposes [Chpca 3-H and (βMe)Phe I $H_{aromatic}$, (βMe)Phe II $H_{aromatic}$ and (3-Ncp)Ala I 3′-H_A, (βMe)Phe II $H_{aromatic}$ and (3-Ncp)Ala I 6-H_A, (βMe)Phe II $H_{aromatic}$ and (3-Ncp)Ala I NH]. In the average structure the corresponding distances are 3.8, 4.6, 5.2, and 3.5 Å, respectively, which reasonably agree with the measured ROE values. There is an upfield chemical shift of the β-proton of (βMe)Phe II (3.04 ppm) compared with that of the corresponding proton in (βMe)Phe I (3.72 ppm), which can be explained by the anisotropy effect of the pyrrole ring. This effect requires a specific folding of the two-residue side chain. Additional anisotropy effects are seen for the methyl protons of the Ile residue exerted by the pyrrole ring of Chpca and for the protons of the (3-Ncp)Ala I side chain by the neighboring aromatic ring of (βMe)Phe I. The large downfield shift of the amide proton of (3-Ncp)Ala II (8.14 ppm) compared with NH of (3-Ncp)Ala I may be due to an H-bonding interaction with the oxygen of Chpca. All amide protons of the macrocyclic ring show low temperature chemical shift values (all $< +/-1$ ppb/°C except NH [(βMe)Phe I]: −3 ppb per °C) indicating shielding from solvent or H-bonding. Data have been submitted to PDB (Protein Data Bank) and BMRB (BioMagResBank).

Biological tests were carried out as described elsewhere.[16b]

Deprotection of *N*-Fmoc-protected amino acids 7a and 7b, and peptides 16 and 17—General procedure (GP 1): The protected amino acids or peptides (1 mmol) were taken up with acetonitrile or THF (2 mL), diethylamine (2 mL) was added, and the resulting mixture left at ambient temperature for 40 min. All volatiles were evaporated under reduced pressure, the residue was taken up with toluene (2 × 5 mL), which was evaporated under reduced pressure to remove the last traces of diethylamine. The obtained crude *N*-deprotected amino acids or peptides were directly used in the next condensation step.

Peptide condensation step for the preparation of dipeptide acids 15a–c—General procedure (GP 2): EDC (1.03 mmol) and HOAt (1.05 mmol) were added to a cooled (4 °C) solution of the *N*-Boc-protected 4-(*Z*)-propenylproline **14** (1 mmol) in anhydrous CH_2Cl_2 (3 mL). After 10 min, the solution of the appropriate crude N_β-deprotected diamino ester (0.97 mmol) and TMP (3 mmol) in anhydrous CH_2Cl_2 (1 mL) was added at the same temperature (in the case of **7c**·HCl two additional equivalents of TMP were used). The temperature was allowed to reach 20 °C, and stirring was continued for 6 h. Then the reaction mixture was diluted with Et_2O or EtOAc (30 mL), and the mixture washed with 1 M $KHSO_4$ (3 × 5 mL), water (2 × 5 mL), saturated aqueous solution of $NaHCO_3$ (3 × 5 mL), water (3 × 5 mL), brine (2 × 5 mL), dried and concentrated under reduced pressure. The residue was purified by column chromatography and recrystallization to give the respective dipeptide esters.

Hydrolysis step for the preparation of dipeptide acids 15a–c—General procedure (GP 3): A 40% aqueous solution of tetra-*n*-butylammonium hydroxide (0.15 mmol) was added dropwise to an ice-cold solution of the respective dipeptide ester (0.10 mmol) in THF (0.91 mL) within 3 min, and stirring was continued at the same temperature for an additional 45 min (TLC monitoring to detect complete consuming of the starting material). A 1 M aqueous H_2SO_4 (0.5 mL) was then added, and the mixture was diluted with Et_2O (50 mL). The organic layer was separated and washed with 1 M $KHSO_4$ (2 × 10 mL), water (5 × 10 mL), brine (2 × 5 mL), dried and filtered. The filtrate was concentrated under reduced pressure to give the crude product which was purified by column chromatography or/and recrystallization.

Peptide condensation step for the preparation of the branched hexapeptides 18a–c—General procedure (GP 4): Tetrapeptide **16** or **17** (0.21 mmol) was deprotected according to GP 1, taken up with anhydrous CH_2Cl_2 (5 mL), the respective dipeptide acid (0.23 mmol), HATU (0.25 mmol) and HOAt (0.23 mmol) were added, and the reaction mixture was cooled to 4 °C. After this, a solution of DIEA (29 mg, 0.22 mmol) and TMP (75 mg, 0.62 mmol) in CH_2Cl_2 (2 mL) were added at the same temperature within 5 min. The temperature was allowed to reach 20 °C, and stirring was continued for an additional 15 h. The crude product obtained after aqueous work-up, according to GP 2, was finally purified by recrystallization and/or column chromatography.

Preparation of *N*-MeZ-protected cyclohexapeptides 19a–c, *epi*-19a and *epi*-19c—General procedure (GP 5): 2M HCl in EtOAc (2 mL) was added to the appropriate branched hexapeptide (0.10 mmol); the reaction mixture was stirred at 20°C for 1 h in a dark place, and was then concentrated under reduced pressure at 20°C. The residue was triturated with anhydrous Et_2O (2×5 mL) to give the hydrochloride of the deprotected material as a colorless solid, which was taken up with anhydrous CH_2Cl_2 (1.0 L). The solution was cooled to 4°C (internal temperature), HATU (0.103 mmol) and HOAt (0.10 mmol) were added, and then a solution of DIEA (0.40 mmol) in CH_2Cl_2 (50 mL) was added over 30 min. The cooling bath was removed and stirring continued for an additional 2 h at ambient temperature. Then the reaction mixture was cooled again to 4°C, and a second portion of each, HATU (0.103 mmol) and HOAt (0.10 mmol), was added, and then a solution of DIEA (0.40 mmol) in CH_2Cl_2 (50 mL) was added within 30 min. The temperature was allowed to reach 20°C, and stirring was continued for 15 h. After this, the solvent was removed under reduced pressure, the residue was taken up with Et_2O, and after the usual aqueous work-up (GP 2) and concentration under reduced pressure, the crude product was purified first by column chromatography and then by recrystallization (Et_2O/pentane) to give a mixture of the epimeric cyclopeptides, which was separated by preparative HPLC to give the respective cyclohexapeptides.

Deprotection of *N*-MeZ protected cyclohexapeptides 19a–c and *epi*-19a—General procedure (GP 6): The *N*-MeZ-protected cyclopeptides (18 μmol) were deprotected by treatment with 10% anisole in TFA (1.1 mL) in the dark at ambient temperature for 2 h. All volatiles were removed under reduced pressure (0.05 Torr) at 20°C. The residues were triturated with hexane (6×5 mL) and dried to give the deprotected materials as trifluoroacetates, which were directly used in the next condensation step.

Deprotection of *O*-MOM protected hormaomycin aza-analogues *O*-MOM-2a–c and *epi*-*O*-MOM-2a—General procedure (GP 7): The respective *O*-MOM protected hormaomycin analogue (15 μmol) was deprotected by treatment with $MgBr_2{\cdot}Et_2O$ (0.30 mmol) and EtSH (0.10 mmol) in CH_2Cl_2 (10 mL) at ambient temperature for 3 h. The mixture was taken up with Et_2O (40 mL) and washed with 1N $KHSO_4$ (3×10 mL), water (4×10 mL), brine (2×5 mL), dried, filtered and concentrated under reduced pressure. The residue was recrystallized from CH_2Cl_2/pentane to give the respective hormaomycin analogue, which, if necessary, was further purified by preparative HPLC. The fraction containing the desired product was collected, and its pH value was carefully adjusted to 6.9 (pH meter) with diluted aqueous ammonia, and then it was lyophilized. The residue was dissolved in EtOAc (10 mL), the solution was washed with water (3×5 mL), dried and filtered. Removal of the solvent under reduced pressure gave the pure hormaomycin aza-analogue.

Methyl (2*R*,3*R*)-2-amino-3-(9-fluorenylmethyloxycarbonylamino)butyrate hydrochloride: Boc-*a*-Dab(Fmoc)-O*t*Bu **5** (0.39 g, 0.79 mmol) was deprotected with TFA (5 mL) for 1 h. All volatiles were removed under reduced pressure at 20°C. The solid residue was taken up with 1M HCl (5 mL) and methanol (20 mL) and after 10 min the mixture was concentrated to give the crude H-*a*-Dab(Fmoc)-OH·HCl (0.31 g, 100%), which was dried at 0.02 Torr at ambient temperature for 16 h, and used for the next step without further purification. $SOCl_2$ (0.60 mL, 8.27 mmol) was added dropwise to a solution of the crude amino acid hydrochloride (0.31 g, max 0.79 mmol) in anhydrous methanol (35 mL) at −20°C for 5 min and stirring was continued at the same temperature for an additional 15 min. The mixture was then allowed to warm to 20°C, and, after stirring at this temperature for 1 h, the reaction flask was sealed, and the mixture was heated t 50°C with stirring for an additional 20 h. The reaction mixture was then concentrated under reduced pressure, and the residue was triturated with Et_2O to give the crude title compound (0.29 g, max. 94%) as a colorless solid. R_f=0.30 (MeOH/$CHCl_3$ 1:100); ^{1}H NMR (250 MHz, CD_3OD): δ=1.36 (d, J=7 Hz, 3H, H-4), 3.97 (s, 3H, OMe), 4.16–4.34 (m, 3H, 2-H and 9″-H, 1′-H_a), 4.40–4.59 (m, 2H, 3-H, 1′-H_b), 7.27–7.50 (m, 4H, Ar-H), 7.54 (d, J=6.8 Hz, 1H, NH), 7.70 (d, J=7.3 Hz, 2H, Ar-H), 7.84 (d, J=7.3 Hz, 2H, Ar-H).

MeZ-*a*-Dab(Fmoc)-OMe (6): $NaHCO_3$ (0.156 g, 1.85 mmol) and then a solution of MeZOSu (0.244 g, 0.93 mmol) in acetone (5 mL) were added to a vigorously stirred solution of H-*a*-Dab(Fmoc)-OMe·HCl (0.29 g, max. 0.74 mmol) in water (7 mL), and stirring was continued for 90 min (if a precipitate formed, acetone and/or water was added to obtain a homogeneous solution). The mixture was then concentrated under reduced pressure, diluted with water (40 mL), and the resultant suspension was filtered. The crude product was washed with Et_2O/pentane 1:1 (50 mL), water (100 mL), 3% $NaHCO_3$ (50 mL), water (20 mL), 1M HCl, water (50 mL), pentane (50 mL), dried and finally recrystallized from CH_2Cl_2/hexane to give **6** (0.272 g, 69% over three steps) as a colorless solid. M.p. 167–168°C; $[\alpha]_D^{20}$=8.5 (c=0.40, THF); ^{1}H NMR (250 MHz, $CDCl_3$): δ=1.47 (d, J=6.8 Hz, 3H, 4-H), 2.34 (s, 3H, 1′-H, *MeZ*), 3.77 (s, 3H, OMe), 4.10–4.51 (m, 4H, 3-H and 9′-H, 1-H, *Fmoc*), 4.60 (dd, J=8.1, 3.1 Hz, 1H, 2-H), 5.08 (s, 2H, Bzl-H), 5.32 (d, J=8.0 Hz, 1H, NH), 5.67 (d, J=6.8 Hz, 1H, NH), 7.16 (d, J=7.3 Hz, 2H, Ar-H), 7.21–7.46 (m, 6H, Ar-H), 7.61 (d, J=6.8 Hz, 2H, Ar-H), 7.77 (d, J=7.3 Hz, 2H, Ar-H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=16.3 (+, C-4), 21.0 (+, C-1′, *MeZ*), 47.0 (+, C-3), 48.9 (+, C-9′, *Fmoc*), 52.5 (+, OMe), 57.8 (+, C-2), 66.8 (−, Bzl-H, *MeZ*), 67.1 (−, C-1, *Fmoc*), 119.8, 125.0, 126.9, 127.5, 128.3, 129.1 (+, Ar-C), 132.8 (C_{quat}, Ar-C), 137.9 (C_{quat}, Ar-C), 141.1 (C_{quat}, Ar-C), 143.7, 143.9 (C_{quat}, Ar-C), 155.8, 156.4 (C_{quat}, NCO_2), 170.7 (C_{quat}, C-1); IR (KBr): $\tilde{\nu}$=3316, 3067, 2948, 1748, 1691, 1542, 1450, 1338, 1316, 1282, 1231, 1169 cm^{-1}; MS (EI, 70 eV): m/z (%): 502 (1) [M^+], 266 (10) [$C_{14}H_{20}NO_4^+$], 178 (100) [$C_{14}H_{10}^+$], 165 (5), 105 (22) [$C_8H_9^+$], 44 (11) [CO_2^+]; HRMS (EI): m/z: calcd for $C_{29}H_{30}N_2O_6$: 502.2104, correct mass found; elemental analysis calcd (%) for $C_{29}H_{30}N_2O_6$ (502.6): C 69.31, H 6.02, N 5.57; found C 69.08, H 5.88, N 5.38.

Methyl (2*S*,3*R*)-3-(benzyloxycarbonyl-*N*-methylamino)-2-hydroxybutyrate: A solution of the *O*-TBDMS, NMe-Z protected *tert*-butyl ester of (*S*)-isothreonine **8** (0.73 g, 1.67 mmol) in MeCN (38 mL) was treated with 5% aqueous HF (40 mL) at 4°C for 10 min. The mixture was allowed to warm to 20°C, and stirring was continued for an additional 4 h. A saturated aqueous solution of $NaHCO_3$ was then carefully added to adjust the pH value to about 8, and the mixture was extracted with Et_2O (2×50 mL). The organic fraction was washed with water (5×20 mL), brine (2×10 mL), dried, filtered and concentrated under reduced pressure. The resultant crude alcohol was dried at 0.02 Torr for 2 h and then deprotected by treatment with TFA (6 mL). After 1 h, all volatiles were removed under reduced pressure, the residue was dissolved in toluene (2×20 mL), which was distilled off to remove the last traces of TFA to give the crude (2*S*,3*R*)-3-(benzyloxycarbonyl-*N*-methylamino)-2-hydroxybutyric acid (0.42 g, max. 94%). It was dried at 0.02 Torr and ambient temperature for 2 h, then taken up with Et_2O (10 mL; some methanol was added to obtain a homogeneous solution) and the mixture was treated with an excess of an ethereal solution of diazomethane untill a yellow coloration of the reaction mixture persisted. The mixture was then concentrated under reduced pressure, and the residue was purified by column chromatography to give the title compound (0.361 g, 71% over two steps; R_f=0.22, EtOAc/hexane 1:3) as a turbid oil, which was directly used for the next step without any further characterization.

Methyl (2*S*,3*R*)-2-azido-3-(benzyloxycarbonyl-*N*-methylamino)butyrate (9): Mesyl chloride (0.14 mL, 1.81 mmol) was added dropwise to a solution of the NMe-Z protected (*S*)-isothreonine methyl ester (0.36 g, 1.28 mmol) and TEA (0.254 mL, 1.81 mmol) in CH_2Cl_2 (7 mL) at −30°C for 3 min, and stirring was continued at the same temperature for 1 h. The reaction mixture was then allowed to warm to 4°C and stirred at this temperature for an additional 1 h. Finally, the cooling bath was removed, and stirring was continued for an additional 3 h. Saturated aqueous solution of $NaHCO_3$ (3 mL) was then added, and the mixture was taken up with Et_2O (50 mL). After the usual aqueous work-up (GP 2) the organic layer was dried, filtered and concentrated under reduced pressure to give the crude mesylate of NMe-Z protected (*S*)-isothreonine methyl ester (0.46 g, 100%; R_f=0.11, EtOAc/hexane 1:6) as a colorless oil. NaN_3 (0.086 g, 1.32 mmol) was added to a solution of this compound (0.46 g, 1.28 mmol) in DMF (8 mL), and stirring continued at 70°C for 15 h. The mixture was then cooled, concentrated under reduced pressure, and the residue was taken up with Et_2O (50 mL). After the usual aqueous work-up (GP 2) the organic layer was dried, filtered and concentrated under

reduced pressure. The resultant crude product was purified by column chromatography (EtOAc/hexane 1:6, $R_f = 0.19$) to give **9** (0.191 g, 49% over two steps) as a mobile colorless oil, which was directly used for the next step without any further characterization.

Boc-*a*-N$_\beta$Dab(Fmoc)-OMe: Ph_3P (0.262 g, 1.00 mmol) was added to a solution of **9** (0.191 g, 0.62 mmol) in THF/H_2O (20:1) (15.8 mL), the resultant mixture was stirred for 24 h. Boc_2O (0.272 g, 1.25 mmol) was then added, and stirring was continued for an additional 24 h. The mixture was then concentrated, and the residue was purified by column chromatography (twice, hexane 1:4, $R_f = 0.22$) to give the N_β-methylated Boc-*a*-Dab(Z)-OMe (0.135 g, 57%) as a viscous colorless oil. This material (0.135 g, 0.35 mmol) in EtOAc (7 mL) was hydrogenated at ambient pressure of hydrogen over 10% Pd on charcoal (0.07 g) for 3 h. The mixture was then filtered and concentrated under reduced pressure to give the crude Boc-*a*-N$_\beta$MeDab-OMe (90 mg, 100%), which was immediately used for the next step. FmocOPfp (0.159 g, 0.39 mmol) was added to a solution of this material, TMP (43 mg, 0.35 mmol), and HOAt (10 mg, 74 μmol) in EtOAc (5 mL) were added and stirring was continued for 15 h. The mixture was then diluted with Et_2O (50 mL) and subjected to the usual aqueous work-up (GP 2). The organic layer was dried, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (EtOAc/hexane 1:4, $R_f = 0.22$) to give the N_β-methylated Boc-*a*-Dab(Fmoc)-OMe (0.135 g, 81% over two steps) as a colorless oil, which was directly used for the next step without any further characterization.

MeZ-*a*-N$_\beta$Dab(Fmoc)-OMe (10): Boc-*a*-N$_\beta$Dab(Fmoc)-OMe (0.135 g, 0.29 mmol) was deprotected with 2 M HCl in EtOAc (4 mL) for 3 h. The mixture was then concentrated under reduced pressure, and the residue was dissolved in MeCN (4 mL). TMP (45 mg, 0.37 mmol), DIEA (37 mg, 0.29 mmol) and finally MeZOSu (83 mg, 0.32 mmol) were added to this solution, and it was stirred for 16 h. *N*,*N*-Dimethylaminopropylamine (20 mg, 0.20 mmol) was then added, and after 10 min the mixture was concentrated under reduced pressure. The residue was taken up with Et_2O and subjected to the usual aqueous work-up (GP 2). The organic layer was dried, filtered and concentrated under reduced pressure. The resultant crude product was purified by column chromatography (EtOAc/hexane 1:3, $R_f = 0.30$) to give **10** (0.122 g, 13% overall yield over 10 steps from **8**) as a turbid glass. $[\alpha]_D^{20} = 9.2$ ($c = 0.25$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.16$, 1.25 (2 × d, $J = 6.9$ Hz, 3H, 4-H), 2.33 (s, 3H, 1′-H, *MeZ*), 2.81 (s, 3H, NMe), 3.66 (s, 3H, OMe), 4.12–4.61 (m, 5H, 2-H, 3-H and 9′-H, 1-H, *Fmoc*), 5.06 (d, $J = 5.1$ Hz, 2H, Bzl-H), 5.31, 5.60 (2 × d, $J = 7.5$ Hz, 1H, NH), 7.15 (d, $J = 7.8$ Hz, 2H, 2-H, *MeZ*), 7.24 (d, $J = 7.8$ Hz, 2H, 3-H, *MeZ*), 7.31 (dd, $J = 7.5$, 7.5 Hz, 2H, 3′-H, *Fmoc*), 7.40 (dd, $J = 7.5$, 7.5 Hz, 2H, 4′-H, *Fmoc*), 7.58–7.64 (m, 2H, 2′-H, *Fmoc*), 7.76 (d, $J = 7.2$ Hz, 5′-H, *Fmoc*); ^{13}C NMR (50.3 MHz, $CDCl_3$): $\delta = 14.3$ (+, C-4), 21.0 (+, C-1′, *MeZ*), 28.9 (+, NMe), 47.1 (+, C-3), 52.4 (+, C-2), 52.9 (+, C-9′, *Fmoc*), 56.6 (+, OMe), 67.0 (−, Bzl-H, *MeZ*), 67.5 (−, C-1, *Fmoc*), 119.8, 124.9, 126.9, 127.5, 128.2, 129.1 (+, Ar-C), 133.0 (C_{quat}, Ar-C), 137.9 (C_{quat}, Ar-C), 141.2 (C_{quat}, Ar-C), 143.8, 143.9 (C_{quat}, Ar-C), 155.9, 156.4 (C_{quat}, NCO_2), 170.9 (C_{quat}, C-1); IR (KBr): $\tilde{\nu} = 2951$, 1751, 1725, 1700, 1521, 1451, 1320, 1273, 1242, 1204, 1018 cm^{-1}; MS (ESI pos.): *m*/*z*: 539 (100) [*M*+Na$^+$].

MeZ-(*R*)-Asn-OH (12): $NaHCO_3$ (0.520 g, 6.18 mmol) and then a solution of MeZOSu (0.775 g, 2.97 mmol) in acetone (7 mL) were added to a vigorously stirred solution of D-aspargine (0.442 g, 2.94 mmol) in water (10 mL), and stirring was continued for 3 h (if a precipitate formed, acetone and/or water was added to obtain a homogeneous solution). The mixture was then concentrated under reduced pressure, diluted with water (40 mL) and washed with CH_2Cl_2 (3 × 10 mL). The pH of the water fraction was adjusted to 1–2 with solid $KHSO_4$, the resulting precipitate was filtered off, washed with H_2O (5 × 20 mL), Et_2O (5 × 20 mL) and dried to give **12** (0.75 g, 91%) as a colorless solid. M.p. 181–183 °C; $[\alpha]_D^{20} = 6.5$ ($c = 1.00$, DMF); ^{1}H NMR (250 MHz, [D$_6$]acetone): $\delta = 2.30$ (s, 3H, 1′-H), 2.50–3.55 (br, 3H, CO_2H, $CONH_2$), 2.65–2.85 (m, 2H, 3-H), 4.39–4.53 (m, 1H, 2-H), 5.03 (s, 2H, Bzl-H), 6.39–6.61 (br, 1H, NH), 7.15 (d, $J = 8.0$ Hz, 2H, Ar-H), 7.26 (d, $J = 8.0$ Hz, 2H, Ar-H); ^{13}C NMR (125.7 MHz, [D$_6$]DMSO): $\delta = 20.7$ (+, C-1′), 36.7 (−, C-3), 50.5 (+, C-2), 65.3 (−, Bzl-H), 127.8 (+, Ar-C), 128.8 (+, Ar-C), 133.8 (C_{quat}, Ar-C), 137.0 (C_{quat}, Ar-C), 155.7 (C_{quat}, NCO_2), 170.7 (C_{quat}, C-1), 173.0 (C_{quat}, C-4); IR (KBr): $\tilde{\nu} = 3419$, 3355, 3214, 3099, 3030, 2989, 2973, 2929, 2827, 2741, 2629, 2533, 1721, 1692, 1645, 1586, 1526, 1346, 1237, 1199, 1183, 1154, 1126 cm^{-1}; MS (EI, 70 eV), *m*/*z* (%): 280 (20) [*M*$^+$], 263 (3) [*M*$^+$ −OH], 159 (8) [$C_5H_7N_2O_4^+$], 122 (46) [$C_8H_{10}O^+$], 105 (100) [$C_8H_9^+$], 87 (16) [$C_3H_7N_2O^+$], 77 (10) [$C_6H_5^+$], 44 (6) [CO_2^+]; elemental analysis calcd (%) for $C_{13}H_{16}N_2O_5$ (280.3): C 55.71, H 5.75, N 9.99; found C 55.97, H 5.73, N 10.08.

MeZ-Dap-OH (13): Iodobenzene bis(trifluoroacetate) (1.46 g, 3.40 mmol) and **12** were suspended by stirring in 50% (*v*/*v*) aqueous DMF (20 mL). After 15 min, pyridine (0.367 g, 4.64 mmol) was added, and the mixture was stirred for an additional 5 h. The emulsion formed was evaporated at 40–45 °C under reduced pressure. The residue was taken up with water (2 × 15 mL), which was evaporated under reduced pressure. The residual oil was taken up in water (50 mL) and washed with chloroform (3 × 10 mL). The aqueous layer was once more concentrated in vacuo, and the residue was dissolved in ethanol (20 mL). The pH value was adjusted to about 7 with pyridine, and the formed suspension was left at 4 °C for 12 h. The precipitate was filtered off and washed with ether (5 × 20 mL) to give, after drying, amino acid **13** (0.51 g, 87%) as a colorless powder. $R_f = 0.32$ (MeCN/AcOH/H_2O 10:1:1); m.p. 210–216 °C (decomp.); $[\alpha]_D^{20} = 38.1$ ($c = 0.31$, 0.1 N HCl); ^{1}H NMR (300 MHz, DCl in D_2O): $\delta = 2.28$ (s, 3H, 1′-H), 3.28 (dd, $J = 12.6$, 9.6 Hz, 1H, 3-H$_a$), 3.49 (dd, $J = 12.6$, 4.5 Hz, 1H, 3-H$_b$), 4.44–4.55 (m, 1H, 2-H), 5.07 (s, 2H, Bzl-H), 7.22 (d, $J = 7.5$ Hz, 2H, Ar-H), 7.28 (d, $J = 7.5$ Hz, 2H, Ar-H); IR (KBr): $\tilde{\nu} = 3303$, 3250–2300, 1695, 1658, 1623, 1592, 1540, 1413, 1273, 1022 cm^{-1}; MS (ESI pos.): *m*/*z*: 275 (86) [*M*+Na$^+$], 253 (12) [*M*+H$^+$]; neg.: *m*/*z*: 251 (10) [*M*−H$^-$]; elemental analysis calcd (%) for $C_{12}H_{16}N_2O_4$ (252.3): C 57.13, H 6.39, N 11.10; found C 56.95, H 6.20, N 10.97.

MeZ-Dap-OMe·HCl (7c·HCl): To a solution of thionyl chloride (0.52 mL, 7.26 mmol) in anhydrous MeOH (10 mL) at −20 °C was added with stirring after 10 min the amino acid **13** (0.50 g, 1.98 mmol). The resulting thick suspension was stirred at 20 °C for 24 h to give a clear solution, which was then left at −28 °C for 16 h. Et_2O (40 mL) was added to complete the precipitation, and the solid was filtered off to give **7c**·HCl (0.47 g, 78%) as long colorless needles. The mother liquor was concentrated, and the residue was recrystallized from MeOH/Et_2O to give a second crop of **7c**·HCl (26 mg, 83% overall yield). M.p. 159–161 °C; $[\alpha]_D^{20} = 32.3$ ($c = 0.86$, DMSO); ^{1}H NMR (250 MHz, [D$_6$]DMSO): $\delta = 2.28$ (s, 3H, 1′-H), 2.98–3.29 (m, 2H, 3-H), 3.66 (s, 3H, OMe), 4.43 (ddddd, $J = 4.3$ Hz, 1H, 2-H), 5.08 (s, 2H, Bzl-H), 7.17 (d, $J = 7.9$ Hz, 2H, Ar-H), 7.25 (d, $J = 7.9$ Hz, 2H, Ar-H), 7.52 (d, $J = 8.3$ Hz,1H, CON*H*), 8.15–8.55 (br, 3H, NH_2·HCl); ^{13}C NMR (125.7 MHz, [D$_6$]DMSO): $\delta = 21.0$ (+, C-1′), 39.2 (−, C-3), 52.0 (+, C-2), 52.8 (+, OMe), 66.0 (−, Bzl-H), 128.2 (+, Ar-C), 129.1 (+, Ar-C), 133.8 (C_{quat}, Ar-C), 137.4 (C_{quat}, Ar-C), 156.3 (C_{quat}, NCO_2), 173.6 (C_{quat}, C-1); IR (KBr): $\tilde{\nu} = 3322$, 3031, 2884, 2621, 1734, 1690, 1597, 1535, 1307, 1264, 1230, 1015 cm^{-1}; MS (ESI pos.): *m*/*z*: 289 (38) [*M*+Na$^+$], 267 (93) [*M*+H$^+$]; elemental analysis calcd (%) for $C_{13}H_{19}N_2O_4Cl$ (302.8): C 51.57, H 6.33, N 9.25; found C 51.29, H 6.48, N 9.11.

MeZ-*a*-Dab[Boc-(4-Pe)Pro]-OMe: Compound **7a** (0.191 g, 0.38 mmol) was deprotected according to GP 1, and the resulting crude N_α-protected diamino ester was coupled with the *N*-Boc protected 4-(*Z*)-propenylproline **14** (0.100 g, 0.39 mmol) by treatment with EDC (77 mg, 0.40 mmol), HOAt (55 mg, 0.41 mmol) and TMP (0.142 g, 1.17 mmol) in CH_2Cl_2 (4 mL) according to GP 2 for 16 h. The crude product obtained after the usual aqueous work-up (GP 2) was finally purified by column chromatography (EtOAc/hexane 1:1.5, $R_f = 0.35$) to give the title compound (0.163 g, 83%) as a turbid oil, which solidified during drying at 60 °C (0.02 Torr) to a colorless solid. M.p. 94–95 °C; $[\alpha]_D^{20} = -41.6$ ($c = 0.32$, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 1.04$–1.19 (m, 3H, 4-H, *a-Dab*), 1.41 [s, 9H, C(CH$_3$)$_3$], 1.64 [dd, $J = 7.0$, 1.5 Hz, 3H, 3′-H, (*4-Pe*)*Pro*], 1.72–2.00 [m, 1H, 3-H$_a$, (*4-Pe*)*Pro*], 2.34 (s, 3H, 1′-H, *MeZ*), 2.34–2.54 [m, 1H, 3-H$_b$, (*4-Pe*)*Pro*], 2.92–3.15 [m, 2H, 4-H, 5-H$_a$, (*4-Pe*)*Pro*], 3.76 (s, 3H, OMe), 3.80–3.96 [m, 1H, 5-H$_b$, (*4-Pe*)*Pro*], 4.03–4.22 (m, 1H, 3-H, *a-Dab*), 4.35–4.57 (m, 2H, 2-H), 5.01 (d, $J = 12.3$ Hz, 1H, Bzl-H$_a$), 5.09 (d, $J = 12.3$ Hz, 1H, Bzl-H$_b$), 5.20–5.37 [m, 1H, 1′-H, (*4-Pe*)*Pro*], 5.54 [dq,

J=10.0, 7.0 Hz, 1H, 2′-H, (*4-Pe*)*Pro*], 5.59–5.77, 6.20–6.40 (2×m, 1H, NH), 6.81 (d, J=8.8 Hz, 1H, NH), 7.15 (d, J=7.8 Hz, 2H, Ar-H), 7.25 (d, J=7.8 Hz, 2H, Ar-H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=13.0 [+, C-3′, (*4-Pe*)*Pro*], 15.3, 16.8 (+, C-4, *a-Dab*), 21.0 (+, C-1′, *MeZ*), 28.1 [+, $C(CH_3)_3$], 35.8 [+, C-4, (*4-Pe*)*Pro*], 37.8 [−, C-3, (*4-Pe*)*Pro*], 46.6, 47.1 (+, C-3, *a-Dab*), 52.0 [−, C-5, (*4-Pe*)*Pro*], 52.4 (+, OMe), 57.5 (+, C-2, *a-Dab*), 60.9, 61.5 [+, C-2, (*4-Pe*)*Pro*], 66.8, 67.2 (−, Bzl-H, *MeZ*), 80.2 [C_{quat}, $C(CH_3)_3$], 126.4 [+, C-2′, (*4-Pe*)*Pro*], 128.2, 129.0 (+, Ar-C), 129.4 [+, C-1′, (*4-Pe*)*Pro*], 132.7, 137.8 (C_{quat}, Ar-C), 154.2, 156.5 (C_{quat}, NCO_2), 170.2, 171.0 (C_{quat}, C-1), 172.0, 172.3 (C_{quat}, C-1); IR (KBr): $\tilde{\nu}$= 3012, 2978, 2929, 2869, 1728, 1703, 1678, 1541, 1519, 1394, 1368, 1259, 1212, 1162 cm^{-1}; MS (EI, 70 eV): *m/z* (%): 517 (1) [M^+], 444 (3)[$M^+-C_4H_9O$], 416 (6) [$M^+-C_5H_9O_2$], 281 (52) [$C_{15}H_{24}N_2O_3^+$], 238 (15) [$C_{13}H_{20}N_2O_3^+$], 225 (32) [$C_{11}H_{16}N_2O_3^+$], 182 (11), 154 (100) [$C_8H_{12}NO_2^+$], 110 (88) [$C_7H_{12}N^+$], 105 (70) [$C_8H_9^+$], 57 (49) [$C_4H_9^+$], 44 (68) [CO_2^+]; HRMS (EI): *m/z*: calcd for $C_{27}H_{39}N_3O_7$: 517.2788, correct mass found; elemental analysis calcd (%) for $C_{27}H_{39}N_3O_7$ (517.6): C 62.65, H 7.59, N 8.12; found C 62.48, H 7.35, N 7.90.

MeZ-*a*-Dab[Boc-(4-Pe)Pro]-OH (15a): A solution of the dipeptide ester MeZ-*a*-Dab[Boc-(4-Pe)Pro]-OMe (0.145 g, 0.28 mmol) in THF (1.8 mL) was hydrolyzed according to GP 3 by treatment with 40% aqueous solution of tetra-*n*-butylammonium hydroxide (0.545 g, 0.84 mmol). The crude product obtained after the usual aqueous work-up (GP 3) was recrystallized from Et_2O/hexane to give acid **15a** (0.108 g, 76%) as a colorless solid. The mother liquor was concentrated under reduced pressure, and the residue was recrystallized twice from Et_2O/hexane to give a second crop of **15a** (0.012 g, 85% overall yield). R_f=0.06 (EtOAc/hexane 1:2, 1.5% AcOH); ^{1}H NMR (250 MHz, $CDCl_3$): δ=1.13–1.47 (m, 3H, 4-H, *a-Dab*), 1.35, 1.39 [2×s, 9H, $C(CH_3)_3$], 1.64 [d, J=5.8 Hz, 3H, 3′-H, (*4-Pe*)*Pro*], 1.73–2.00 [m, 1H, 3-H_a, (*4-Pe*)*Pro*], 2.33 (s, 3H, 1′-H, *MeZ*), 2.33–2.57 [m, 1H, 3-H_b, (*4-Pe*)*Pro*], 2.87–3.20 [m, 2H, 4-H, 5-H_a, (*4-Pe*)*Pro*], 3.48–3.73, 3.73–3.95 [2×m, 1H, 5-H_b, (*4-Pe*)*Pro*], 4.07–4.29 (m, 1H, 3-H, *a-Dab*), 4.41 (d, J=6.5 Hz, 1H, 2-H), 4.43–4.69 (m, 1H, 2-H), 5.03 (s, 2H, Bzl-H), 5.18–5.33 [m, 1H, 1′-H, (*4-Pe*)*Pro*], 5.53 [dq, J=10.8, 7.0 Hz, 1H, 2′-H, (*4-Pe*)*Pro*], 5.83–6.02, 6.31–6.48 (2×m, 1H, NH), 6.81 (d, J=8.8 Hz, 1H, NH), 7.14 (d, J=8.0 Hz, 2H, Ar-H), 7.21–7.38 (br, 1H, CO_2H), 7.23 (d, J=8.0 Hz, 2H, Ar-H).

MeZ-N$_\beta$Me-*a*-Dab[Boc-(4-Pe)Pro]-OMe: Compound **7b** (0.108 g, 0.21 mmol) was deprotected according to GP 1, and the resultant crude monodeprotected diamino ester was coupled with the *N*-Boc protected 4-(*Z*)-propenylproline **14** (64 mg, 0.25 mmol) by using EDC (48 mg, 0.25 mmol), HOAt (34 mg, 0.25 mmol) and TMP (76 mg, 0.63 mmol) in CH_2Cl_2 (3 mL) according to GP 2 for 16 h. The crude product, obtained after the usual aqueous work-up (GP 2), was finally purified by column chromatography (EtOAc/hexane 1:1.5, R_f=0.35) to give the title compound (0.104 mg, 93%) as a turbid oil. Analytical HPLC: gradient 20 → 90% MeCN in water (0.1% TFA) for 35 min, flow rate=0.5 mL min^{-1}, t_R=26.01 min, purity > 97%; $[\alpha]_D^{20}$=12.0 (c=0.35, $CHCl_3$); ^{1}H NMR (300 MHz, $C_2D_2Cl_4$, 373 K): δ=1.31 (d, J=7.2 Hz, 3H, 4-H, *NMe-a-Dab*), 1.42 [s, 9H, $C(CH_3)_3$], 1.50–1.74 [m, 1H, 3-H_a, (*4-Pe*)*Pro*], 1.67 [dd, J=7.2, 1.8 Hz, 3H, 3′-H, (*4-Pe*)*Pro*], 2.26–2.44 [m, 1H, 3-H_b, (*4-Pe*)*Pro*], 2.36 (s, 3H, 1′-H, *MeZ*), 2.90 (s, 3H, NMe), 3.01–3.21 [m, 2H, 4-H, 5-H_a, (*4-Pe*)*Pro*], 3.23–3.48 [m, 0.5H, 5-H_b, (*4-Pe*)*Pro*], 3.74 (s, 3H, OMe), 4.47 (dd, J=7.8, 7.8 Hz, 1H, 3-H, *NMe-a-Dab*), 4.57 (dd, J=7.8, 7.8 Hz, 1H, 2-H, *NMe-a-Dab*), 4.50–4.95 [m, 1H, C-2, (*4-Pe*)*Pro*], 5.08 (s, 2H, Bzl-H), 5.25–5.36 [m, 1H, 1′-H, (*4-Pe*)*Pro*], 5.50–5.85 (br, 1H, NH), 5.54 [dq, J=11.4, 7.2 Hz, 1H, 2′-H, (*4-Pe*)*Pro*], 7.15 (d, J=7.8 Hz, 2H, Ar-H), 7.23 (d, J=7.8 Hz, 2H, Ar-H); the signal of OMe overlapped with the signal of 0.5H, 5-H_b of the (*4-Pe*)*Pro* moiety; ^{13}C NMR (75.5 MHz, $C_2D_2Cl_4$, 373 K): δ=12.7 [+, C-3′, (*4-Pe*)*Pro*], 14.5 (+, C-4, *NMe-a-Dab*), 20.7 (+, C-1′, *MeZ*), 28.2 (+, $C(CH_3)_3$, NMe), 36.0 [+, C-4, (*4-Pe*)*Pro*], 51.9 [−, C-5, (*4-Pe*)*Pro*], 52.1 (+, C-2, *NMe-a-Dab*), 57.2 (+, OMe), 66.7 (−, Bzl-H, *MeZ*), 79.3 [C_{quat}, $C(CH_3)_3$], 125.8 [+, C-2′, (*4-Pe*)*Pro*], 127.7, 128.8 (+, Ar-C), 130.0 [+, C-1′, (*4-Pe*)*Pro*], 133.3, 137.5 (C_{quat}, Ar-C), 153.5, 155.6 (C_{quat}, NCO_2), 170.6, 173.2 (C_{quat}, C-1); the signals of C-2, C-3 of (*4-Pe*)*Pro* and C-3 of *NMe-a-Dab* were unobservable because of their low intensity; IR (KBr): $\tilde{\nu}$=2977, 1751, 1728, 1700, 1521, 1402, 1281, 1163 cm^{-1}; MS (ESI): pos.: *m/z* (%): 554 (100) [M+Na^+]; elemental analysis calcd (%) for $C_{28}H_{41}N_3O_7$ (531.7): C 63.26, H 7.77, N 7.90; found C 62.95, H 7.70, N 7.70.

MeZ-N$_\beta$Me-*a*-Dab[Boc-(4-Pe)Pro]-OH (15b): A solution of the dipeptide ester MeZ-N$_\beta$Me-*a*-Dab[Boc-(4-Pe)Pro]-OMe (0.128 g, 0.24 mmol) in THF (2.0 mL) was hydrolyzed according to GP 3 by treatment with 40% aqueous solution of tetra-*n*-butylammonium hydroxide (0.24 g, 0.36 mmol). The crude product obtained after the usual aqueous work-up (GP 3) was recrystallized three times from hexane and once from Et_2O/hexane to give **15b** (91 mg, 73%) as an extremely viscous turbid oil (R_f= 0.14, acetone/hexane 2:5). $[\alpha]_D^{20}$=8.9 (c=0.37, $CHCl_3$); MS (ESI): pos.: *m/z* (%): 562 (100) [$M-H^+$+2Na^+], 540 (8) [M+Na^+]; neg.: *m/z* (%): 516 (100) [$M-H^-$].

MeZ-Dap[Boc-(4-Pe)Pro]-OMe: Compound **7c** (0.127 g, 0.42 mmol) was coupled with the *N*-Boc protected (4-propenyl)proline **14** (0.11 g, 0.431 mmol) by treatment with EDC (85 mg, 0.44 mmol), HOAt (60 mg, 0.44 mmol) and TMP (0.314 g, 2.59 mmol) in CH_2Cl_2 (5 mL) according to GP 2 for 16 h. The crude product obtained after the usual aqueous work-up (GP 2) was further purified by column chromatography (acetone/hexane 1:2.5, R_f=0.13) to give an oily residue which was triturated with pentane to furnish the title compound (0.14 g, 66%) as a colorless solid. The mother liquor was cooled to 4°C, and the precipitate was filtered off to give a second crop of the title compound (10 mg, 71% overall yield). M.p. 160–162°C; $[\alpha]_D^{20}$=−41.4 (c=0.35, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.40 [s, 9H, $C(CH_3)_3$], 1.64 [dd, J=6.9, 1.8 Hz, 3H, 3′-H, (*4-Pe*)*Pro*], 1.78–2.04 [m, 1H, 3-H_a, (*4-Pe*)*Pro*], 2.11–2.57 [m, 1H, 3-H_b, (*4-Pe*)*Pro*], 2.34 (s, 3H, 1′-H, *MeZ*), 2.97–3.15 [m, 1H, 4-H, (*4-Pe*)*Pro*], 2.99 [dd, J=9.3 Hz, 5-H_a, (*4-Pe*)*Pro*], 3.51–3.92 [m, 3H, 3-H, *Dap*, 5-H_b, (*4-Pe*)*Pro*], 3.75 (s, 3H, OMe), 4.12 (dd, J=8.1 Hz, 1H, 2-H, *Dap*), 4.34–4.51 [m, 1H, 2-H, (*4-Pe*)*Pro*], 5.02 (d, J=12.3 Hz, 1H, Bzl-H_a), 5.08 (dq, J=12.3 Hz, 1H, Bzl-H_b), 5.17–5.30 [m, 1H, 1′-H, (*4-Pe*)*Pro*], 5.52 [dq, J=10.5, 6.9 Hz, 1H, 2′-H, (*4-Pe*)*Pro*], 5.74–6.17 (br, 1H, NH), 6.43–6.85 (br, 1H, NH), 7.14 (d, J=8.1 Hz, 2H, Ar-H), 7.33 (d, J=8.1 Hz, 2H, Ar-H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=13.2 [+, C-3′, (*4-Pe*)*Pro*], 21.2 (+, C-1′, *MeZ*), 28.3 [+, $C(CH_3)_3$], 36.0 [+, C-4, (*4-Pe*)*Pro*], 38.1 [−, C-3, (*4-Pe*)*Pro*], 40.8, 41.5 (−, C-3, *Dap*), 52.4 [−, C-5, (*4-Pe*)*Pro*], 52.7 (+, OMe), 54.3 (+, C-2, *Dap*), 60.8, 61.4 [+, C-2, (*4-Pe*)*Pro*], 67.0 (−, Bzl-H, *MeZ*), 80.7 [C_{quat}, $C(CH_3)_3$], 126.5 [+, C-2′, (*4-Pe*)*Pro*], 128.3 (+, Ar-C), 129.1 (+, Ar-C), 129.4 [+, C-1′, (*4-Pe*)*Pro*], 133.2 (C_{quat}, Ar-C), 137.9 (C_{quat}, Ar-C), 154.4, 155.1 (C_{quat}, NCO_2), 156.3 (C_{quat}, NCO_2), 170.2, 171.0 (C_{quat}, C-1), 170.9, 173.0 (C_{quat}, C-1); IR (KBr): $\tilde{\nu}$=3013, 2977, 2953, 2876, 1747, 1728, 1521, 1367, 1259, 1209, 1162, 1118 cm^{-1}; MS (EI, 70 eV): *m/z* (%): 503 (4) [M^+], 447 (2) [$M^+-C_4H_8$], 402 (11) [$M^+-C_5H_9O_2$], 210 (15) [$C_{10}H_{14}N_2O_3^+$], 154 (100) [$C_8H_{12}NO_2^+$], 110 (84) [$C_7H_{12}N^+$], 105 (56) [$C_8H_9^+$], 57 (38) [$C_4H_9^+$], 41 (5) [$C_3H_5^+$]; elemental analysis calcd (%) for $C_{26}H_{37}N_3O_7$ (503.6): C 62.01, H 7.41, N 8.34; found C 62.09, H 7.20, N 8.10.

MeZ-Dap[Boc-(4-Pe)Pro]-OH (15c): A solution of the dipeptide ester MeZ-Dap[Boc-(4-Pe)Pro]-OMe (0.13 g, 0.26 mmol) in THF (2.0 mL) was hydrolyzed according to GP 3 by treatment with 40% aqueous solution of tetra-*n*-butylammonium hydroxide (0.20 g, 0.31 mmol). The crude product obtained after the usual aqueous work-up (GP 3) was finally purified by column chromatography [acetone/hexane 4:7 (2% AcOH), R_f= 0.36] to give acid **15c** (0.126 g, 99%) as an extremely viscous turbid oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ=1.31, 1.41 [2×s, 9H, $C(CH_3)_3$], 1.65 [d, J=6.0 Hz, 3H, 3′-H, (*4-Pe*)*Pro*], 1.75–1.98 [m, 1H, 3-H_a, (*4-Pe*)*Pro*], 2.33 (s, 3H, 1′-H, *MeZ*), 2.21–2.53 [m, 1H, 3-H_b, (*4-Pe*)*Pro*], 2.93–3.21 [m, 2H, 4-H, 5-H_a, (*4-Pe*)*Pro*], 3.44–3.60 (m, 2H, 3-H, *Dap*), 3.60–4.03 [m, 1H, 5-H_b, (*4-Pe*)*Pro*], 4.03–4.19 [m, 1H, 2-H, (*4-Pe*)*Pro*], 4.21 (dd, J= 7.5 Hz, 1H, 2-H, *Dap*), 4.30–4.39, 4.41–4.54 (2×br, 1H, NH), 5.04 (s, 2H, Bzl-H), 5.15–5.32 [m, 1H, 1′-H, (*4-Pe*)*Pro*], 5.55 [dq, J=10.8, 7.0 Hz, 1H, 2′-H, (*4-Pe*)*Pro*], 6.25 (d, J=6.5 Hz, 1H, NH), 7.12 (d, J=7.5 Hz, 2H, Ar-H), 7.22 (d, J=7.5 Hz, 2H, Ar-H), 7.42–7.65 (br, 1H, CO_2H); MS (ESI): pos.: *m/z* (%): 534 (100) [$M-H$+2Na^+], 512 (45) [M+Na^+]; neg.: *m/z* (%): 488 (100) [$M-H^-$].

MeZ-*a*-Dab[Boc-(4-Pe)Pro]-(βMe)Phe-(*R*)-(3-Ncp)Ala-(βMe)Phe-Ile-ODCPM (18a): The tetrapeptide **16** (0.172 g, 0.19 mmol), after removal of the Fmoc group according to GP 1, was coupled with the dipeptide acid **15a** (0.104 g, 0.21 mmol) by treatment with HATU (79 mg,

0.21 mmol), HOAt (30 mg, 0.22 mmol) and TMP (75 mg, 0.62 mmol) in CH_2Cl_2 (5 mL) according to GP 4 for 15 h. The mixture was then diluted with Et_2O (50 mL), and subjected to the usual aqueous work-up (GP 2). The organic layer was dried, filtered and concentrated under reduced pressure. The residue was recrystallized from hexane, then purified by column chromatography (EtOAc/hexane 4:3, $R_f = 0.34$) and finally recrystallized from hexane again to give the branched hexapeptide **18a** (0.176 g, 80%) as a colorless solid. M.p. 101–103 °C (decomp.), $[\alpha]_D^{20} = 52.8$ ($c = 0.29$, THF); ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 0.34$ (dddd, $J = 4.8$, 4.8, 4.8, 4.8 Hz, 1H, 2′-H, *DCPM*), 0.40 (dddd, $J = 4.8$, 4.8, 4.8, 4.8 Hz, 1H, 2′-H, *DCPM*), 0.43 (dddd, $J = 4.8$, 4.8, 4.8, 4.8 Hz, 1H, 2′-H, *DCPM*), 0.45–0.54 (m, 2H, 2′-H, *DCPM*), 0.54–0.59 (m, 2H, 2′-H, *DCPM*), 0.66 (ddddd, $J = 4.2$, 4.2, 4.2, 4.2, 4.2 Hz, 1H, 2′-H, *DCPM*), 0.79 (d, $J = 6.6$ Hz, 3H, 1′-H, *Ile*), 0.84–0.92 [m, 1H, 1′-H, (*3-Ncp*)*Ala*] 0.90 (t, $J = 7.2$ Hz, 3H, 5-H, *Ile*), 1.04 [ddd, $J = 6.0$, 7.2, 7.2 Hz, 1H, 3′-H_a, (*3-Ncp*)*Ala*], 1.06–1.14 (m, 1H, 1′-H_a, *DCPM*), 1.14–1.23 (m, 1H, 1′-H_b, *DCPM*), 1.23 [d, $J = 6.6$ Hz, 3H, 4-H, (β*Me*)*Phe*], 1.25 [d, $J = 6.6$ Hz, 3H, 4-H, (β*Me*)*Phe*], 1.28–1.39 [m, 2H, 3-H, (*3-Ncp*)*Ala*], 1.33 (d, $J = 7.2$ Hz, 3H, 4-H, *a-Dab*), 1.34 [s, 9H, $C(CH_3)_3$], 1.45–1.53 [m, 1H, 3′-H_b, (*3-Ncp*)*Ala*], 1.69 [dd, $J = 6.6$, 1.2 Hz, 3′-H, (*4-Pe*)*Pro*], 1.81 [ddd, $J = 12.0$, 12.0, 12.0 Hz, 1H, 3-H_a, (*4-Pe*)*Pro*], 1.85–1.93 (m, 1H, 3-H, *Ile*), 2.32 (s, 3H, 1′-H, *MeZ*), 2.36 [ddd, $J = 12.0$, 6.0, 6.0 Hz, 3-H_b, (*4-Pe*)*Pro*], 3.12–3.23 [m, 2H, 3-H, (β*Me*)*Phe*, 5-H_a, (*4-Pe*)*Pro*], 3.21–3.30 [m, 2H, 3-H, (β*Me*)*Phe*, 4-H, (*4-Pe*)*Pro*], 3.67 [dd, $J = 9.0$, 7.8 Hz, 1H, 5-H_b, (*4-Pe*)*Pro*], 3.89 [ddd, $J = 7.2$, 3.0, 3.0 Hz, 1H, 2′-H, (*3-Ncp*)*Ala*], 4.14 (t, $J = 7.8$ Hz, 1H, 1-H, *DCPM*), 4.22 [dd, $J = 4.8$, 2.4 Hz, 1H, 2-H, (*4-Pe*)*Pro*], 4.24 (dd, $J = 9.6$, 6.6 Hz, 1H, 2-H, *a-Dab*), 4.30 [dd, $J = 10.8$, 6.0 Hz, 1H, 2-H, (β*Me*)*Phe*], 4.34 (dd, $J = 9.3$, 4.5 Hz, 1H, 2-H, *Ile*), 4.60 [ddd, $J = 10.5$, 5.4, 5.4 Hz, 1H, 2-H, (*3-Ncp*)*Ala*], 4.62–4.70 [m, 2H, 2-H, (β*Me*)*Phe*, 3-H, *a-Dab*], 5.00 (d, $J = 12.0$ Hz, Bzl-H_a), 5.06 (d, $J = 12.0$ Hz, Bzl-H_b), 5.26–5.33 [m, 1H, 1′-H, (*4-Pe*)*Pro*], 5.56 [dq, $J = 11.1$, 6.6 Hz, 1H, 2′-H, (*4-Pe*)*Pro*], 6.61 (d, $J = 6.6$ Hz, 1H, NH), 6.97 (d, $J = 10.2$ Hz, 1H, NH), 7.01 (d, $J = 9.0$ Hz, 1H, NH), 7.10 (d, $J = 8.4$ Hz, 2H, Ar-H), 7.16–7.32 (m, 13H, Ar-H, NH), 7.49 (d, $J = 9.6$ Hz, 1H, NH), 7.60 (d, $J = 9.6$ Hz, 1H, NH); the signal of 4-H of the (β*Me*)*Phe* residue (1.23 ppm) overlapped the signal of 4-H_a of the *Ile* fragment, and the signal of C-(CH_3) overlapped the signal of 4-H_b of the *Ile* moiety; ^{13}C NMR (150.8 MHz, $CDCl_3$): $\delta = 2.5$, 2.79, 2.83, 3.0 (−, C-2′, *DCPM*), 11.6 (+, C-5, *Ile*), 13.2 [+, C-3′, (*4-Pe*)*Pro*], 14.1, 14.6 (+, C-1′, *DCPM*), 15.7 (+, C-1′, *Ile*), 18.5 [+, C-4, (β*Me*)*Phe*], 18.6 [−, C-3′, (*3-Ncp*)*Ala*], 19.7 [+, C-4, (β*Me*)*Phe*], 19.9 (+, C-4, *a-Dab*), 21.1 (+, C-1′, *MeZ*), 21.6 [+, C-1′, (*3-Ncp*)*Ala*], 25.2 (−, C-4, *Ile*), 28.3 [+, $C(CH_3)_3$], 30.8 [−, C-3, (*3-Ncp*)*Ala*], 36.2 [−, C-3, (*4-Pe*)*Pro*], 36.5 (+, C-3, *Ile*), 37.1 [+, C-4, (*4-Pe*)*Pro*], 40.2 [+, C-3, (β*Me*)*Phe*], 41.9 [+, C-3, (β*Me*)*Phe*], 46.3 (+, C-3, *a-Dab*), 50.8 [+, C-2, (*3-Ncp*)*Ala*], 52.5 [−, C-5, (*4-Pe*)*Pro*], 56.6 (+, C-2, *Ile*), 59.5 [+, C-2′, (*3-Ncp*)*Ala*], 60.9 (+, C-2, *a-Dab*), 61.5 [+, C-2, (β*Me*)*Phe*], 63.3 [+, C-2, (*4-Pe*)*Pro*], 63.4 [+, C-2, (β*Me*)*Phe*], 66.7 (−, Bzl-C), 80.2 [C_{quat}, $C(CH_3)_3$], 83.1 (+, C-1, *DCPM*), 126.7(+, Ar-C), 127.0 [+, C-2′, (*4-Pe*)*Pro*], 127.4, 127.6, 127.7, 128.39, 128.43, 128.85, 128.88 (+, Ar-C), 129.2 [+, C-1′, (*4-Pe*)*Pro*], 133.5, 137.7, 141.6, 141.7 (C_{quat}, Ar-C), 154.4, 155.9 (C_{quat}, NCO_2), 169.7, 170.9, 173.56, 173.59, 174.06, 174.11 (C_{quat}, C-1); IR (KBr): $\tilde{\nu} = 3087$, 3010, 2973, 2934, 2876, 1730, 1673, 1545, 1513, 1390, 1368, 1162 cm^{-1}; MS (ESI): pos.: *m*/*z* (%): 1212 (100) [*M*+Na^+]; neg.: *m*/*z* (%): 1188 (100) [*M*−H^-]; elemental analysis calcd (%) for $C_{65}H_{88}N_8O_{13}$ (1189.5): C 65.64, H 7.46, N 9.42; found C 65.63, H 7.22, N 9.26.

MeZ-*a*-N$_\beta$Me-Dab[Boc-(4-Pe)Pro]-(βMe)Phe-(*R*)-(3-Ncp)Ala-(βMe)Phe-Ile-OTMSE (18b): The tetrapeptide **17** (77 mg, 0.081 mmol), after removal of the Fmoc group according to GP 1 by treatment with 50% Et_2NH in THF (2 mL), was coupled with the dipeptide acid **15b** (0.55 mg, 0.106 mmol) by using HATU (40.4 mg, 0.106 mmol), HOAt (14.4 mg, 0.106 mmol) and TMP (64 mg, 0.53 mmol) in CH_2Cl_2 (5 mL) according to GP 4 for 15 h. The mixture was then diluted with Et_2O (50 mL), and subjected to the usual aqueous work-up (GP 2). The organic layer was dried, filtered and concentrated under reduced pressure. The residue was recrystallized from *t*BuOMe/hexane, and then purified by column chromatography (acetone/hexane 1:2, $R_f = 0.32$) to give the branched hexapeptide **18a** (91.0 mg, 93%) as an amorphous colorless solid. $[\alpha]_D^{20} = 10.3$ ($c = 0.31$, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 0.09$ [s, 9H, $Si(CH_3)_3$], 0.74 (d, $J = 6.6$ Hz, 3H, 1′-H, *Ile*), 0.90 (t, $J = 7.2$ Hz, 3H, 5-H, *Ile*), 1.04 [ddd, $J = 6.6$, 6.6, 6.6 Hz, 1H, 3′-H_a, (*3-Ncp*)*Ala*], 1.04 (dd, $J = 8.4$, 8.4 Hz, 2H, *TMSE*), 1.09–1.23 [m, 2H, 1′-H, (*3-Ncp*)*Ala*, 4-H_a, *Ile*], 1.26 [d, $J = 6.6$ Hz, 3H, 4-H, (β*Me*)*Phe*], 1.35 [s, 9H, $C(CH_3)_3$], 1.40–1.46 [m, 2H, 3-H_b, 3′-H_b, (*3-Ncp*)*Ala*], 1.49 (d, $J = 7.2$ Hz, 3H, 4-H, *a*-N$_\beta$*Me-Dab*), 1.58 [ddd, $J = 11.4$, 11.4, 11.4 Hz, 1H, 3-H_a, (*4-Pe*)*Pro*], 1.68 [dd, $J = 6.6$, 1.2 Hz, 3′-H, (*4-Pe*)*Pro*], 1.84–1.93 (m, 1H, 3-H, *Ile*), 2.28 [ddd, $J = 11.4$, 6.6, 6.6 Hz, 3-H_b, (*4-Pe*)*Pro*], 2.32 (s, 3H, 1′-H, *MeZ*), 2.93 (s, 3H, NMe, *a*-N$_\beta$*Me-Dab*), 3.15 [dd, $J = 10.5$, 10.5 Hz, 1H, 5-H_a, (*4-Pe*)*Pro*], 3.18–3.28 [m, 1H, 4-H, (*4-Pe*)*Pro*], 3.31–3.40 [m, 2H, 2×H-3, (β*Me*)*Phe*] 3.71 [dd, $J = 10.5$, 7.8 Hz, 1H, 5-H_b, (*4-Pe*)*Pro*], 3.87 [ddd, $J = 6.6$, 3.0, 3.0 Hz, 1H, 2′-H, (*3-Ncp*)*Ala*], 4.12 [dd, $J = 11.4$, 6.6 Hz, 1H, 2-H, (*4-Pe*)*Pro*], 4.19 (d, $J = 4.8$ Hz, 1H, 2-H, *a*-N$_\beta$*Me-Dab*), 4.28 (dd, $J = 8.4$, 8.4, 1-H, *TMSE*), 4.37 [dd, $J = 9.0$, 4.5 Hz, 1H, 2-H, (β*Me*)*Phe*], 4.53 [ddd, $J = 9.6$, 4.8, 4.8 Hz, 1H, 2-H, (*3-Ncp*)*Ala*], 4.65 (dd, $J = 10.5$, 10.5 Hz, 1H, 2-H, *Ile*), 4.75 [dd, $J = 9.9$, 7.5 Hz, 1H, 2-H, (β*Me*)*Phe*], 4.89 (d, $J = 12.0$ Hz, Bzl-H_a), 5.09 (d, $J = 12.0$ Hz, Bzl-H_b), 5.12–5.19 (m, 1H, 3-H, *a*-N$_\beta$*Me-Dab*), 5.22–5.28 [m, 1H, 1′-H, (*4-Pe*)*Pro*], 5.55 [dq, $J = 11.7$, 6.6 Hz, 1H, 2′-H, (*4-Pe*)*Pro*], 6.92 (d, $J = 9.0$ Hz, 1H, NH), 7.10 (d, $J = 8.4$ Hz, 2H, Ar-H, *MeZ*), 7.14–7.28 (m, 11H, Ar-H, NH), 7.22 (d, $J = 8.4$ Hz, 2H, Ar-H, *MeZ*), 7.29 (d, $J = 6.0$ Hz, 1H, NH), 7.61 (d, $J = 9.6$ Hz, 1H, NH), 8.02–8.10 (br, 1H, NH); the signal of 4-H of the (β*Me*)*Phe* (1.30 ppm) residue overlapped the signal of 3-H_a of the (*3-Ncp*)*Ala* moiety, and the signal of $C(CH_3)$ overlapped the signal of 4-H_b of the *Ile* moiety; ^{13}C NMR (150.8 MHz, $CDCl_3$): $\delta = -1.5$ [+, $Si(CH)_3$], 11.7 (+, C-5, *Ile*), 13.2 [+, C-3′, (*4-Pe*)*Pro*], 15.9 (+, C-1′, *Ile*), 16.3 (−, C-2, *TMSE*), 18.3 [−, C-3′, (*3-Ncp*)*Ala*], 18.9 [+, C-4, (β*Me*)*Phe*], 19.6 [+, C-4, (β*Me*)*Phe*], 21.1 (+, C-1′, *MeZ*), 21.8 [+, C-1′, (*3-Ncp*)*Ala*], 25.2 (−, C-4, *Ile*), 28.3 [+, $C(CH_3)_3$], 30.7 (+, NMe, *a*-N$_\beta$*Me-Dab*), 31.3 [−, C-3, (*3-Ncp*)*Ala*], 35.4 [−, C-3, (*4-Pe*)*Pro*], 36.3 [+, C-4, (*4-Pe*)*Pro*], 37.3 (+, C-3, *Ile*), 40.0 [+, C-3, (β*Me*)*Phe*], 41.9 [+, C-3, (β*Me*)*Phe*], 50.3 (+, C-3, *a*-N$_\beta$*Me-Dab*), 50.5 [+, C-2, (*3-Ncp*)*Ala*], 52.3 [−, C-5, (*4-Pe*)*Pro*], 56.2 [+, C-2, (β*Me*)*Phe*], 57.5 [+, C-2, (β*Me*)*Phe*], 59.6 [+, C-2′, (*3-Ncp*)*Ala*], 61.2 (+, C-2, *Ile*), 62.6 [+, C-2, (*4-Pe*)*Pro*], 63.6 (+, C-2, *a*-N$_\beta$*Me-Dab*), 63.9 (−, C-1, *TMSE*), 66.5 (−, Bzl-C), 79.8 [C_{quat}, $C(CH_3)_3$], 126.8 [+, C-2′, (*4-Pe*)*Pro*], 127.05, 127.08, 127.6, 127.9, 128.5, 128.6, 128.7, 128.9, (+, Ar-C), 129.2 [+, C-1′, (*4-Pe*)*Pro*], 133.4, 137.7, 141.2, 142.3 (C_{quat}, Ar-C), 154.1, 155.9 (C_{quat}, NCO_2), 170.2, 170.73, 170.79, 173.0, 174.0, 175.5, (C_{quat}, C-1); IR (KBr): $\tilde{\nu} = 3059$, 2970, 2879, 1660, 1638, 1543, 1400, 1367, 1164 cm^{-1}; MS (ESI): pos.: *m*/*z* (%): 1232 (100) [*M*+Na^+]; neg.: *m*/*z* (%): 1207 (20) [*M*−H^-]; HRMS (ESI): *m*/*z*: calcd for [$C_{64}H_{82}N_8O_{13}SiNa^+$]: 1231.6445; found 1231.6444.

MeZ-Dap[Boc-(4-Pe)Pro]-(βMe)Phe-(*R*)-(3-Ncp)Ala-(βMe)Phe-Ile-ODCPM (18c): The tetrapeptide **16** (0.203 g, 0.22 mmol), after removal of the Fmoc group according to GP 1, was coupled with the dipeptide acid **15c** (0.120 g, 0.25 mmol) by treatment with HATU (93 mg, 0.25 mmol), HOAt (33 mg, 0.25 mmol) and TMP (0.119 g, 0.98 mmol) in CH_2Cl_2 (5 mL) according to GP 4 for 15 h. The mixture was then diluted with Et_2O (50 mL), and subjected to the usual aqueous work-up (GP 2). The organic layer was dried, filtered and concentrated under reduced pressure. The oily residue was purified by column chromatography (acetone/hexane 5:2, $R_f = 0.22$, three times) and finally recrystallized twice from Et_2O/hexane to give the branched hexapeptide **18c** (0.151 g, 59%) as a colorless solid. M.p. 102–103 °C, $[\alpha]_D^{20} = 88.9$ ($c = 0.46$, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 0.33$ (dddd, $J = 4.8$, 4.8, 4.8, 4.8 Hz, 1H, 2′-H, *DCPM*), 0.38 (dddd, $J = 4.8$, 4.8, 4.8, 4.8 Hz, 1H, 2′-H, *DCPM*), 0.41 (dddd, $J = 4.8$, 4.8, 4.8, 4.8 Hz, 1H, 2′-H, *DCPM*), 0.47–0.61 (m, 2H, 2′-H, *DCPM*), 0.54–0.59 (m, 2H, 2′-H, *DCPM*), 0.66 (dddddd, $J = 4.8$, 4.8, 4.8, 4.8, 4.8, 4.8 Hz, 1H, 2′-H, *DCPM*), 0.81 (d, $J = 6.6$ Hz, 3H, 1′-H, *Ile*), 0.91 (t, $J = 7.2$ Hz, 3H, 5-H, *Ile*), 0.92–0.97 [m, 1H, 1′-H, (*3-Ncp*)*Ala*] 1.00 [ddd, $J = 7.2$, 7.2, 7.2 Hz, 1H, 3′-H_a, (*3-Ncp*)*Ala*], 1.04–1.12 (m, 1H, 1′-H_a, *DCPM*), 1.12–1.17 (m, 1H, 1′-H_b, *DCPM*), 1.17–1.22 (m, 1H, 4-H_a, *Ile*), 1.23–1.27 [m, 1H, 3-H_a, (*3-Ncp*)*Ala*], 1.27 [d, $J = 6.6$ Hz, 3H, 4-H, (β*Me*)*Phe*], 1.34 [s, 9H, $C(CH_3)_3$], 1.47–1.54 [m, 1H, 3′-H_b, (*3-Ncp*)*Ala*], 1.68 [dd, $J = 6.6$, 1.2 Hz, 3′-H, (*4-Pe*)*Pro*], 1.81 [ddd, $J = 12.0$, 12.0, 12.0 Hz, 1H, 3-H_a, (*4-Pe*)*Pro*], 1.84–1.92 (m, 1H, 3-H, *Ile*), 2.33 (s, 3H, 1′-H, *MeZ*), 2.35 [ddd, $J = 12.0$, 6.0, 6.0 Hz, 3-H_b, (*4-Pe*)*Pro*], 3.04 (ddd, $J = 13.8$, 2.8, 2.8 Hz, 3-H_a, *Dap*), 3.12–3.21 [m, 2H, 3-H, (β*Me*)*Phe*, 5-H_a, (*4-Pe*)*Pro*], 3.21–3.29 [m, 1H, 4-H, (*4-Pe*)*Pro*], 3.32 [dq, $J = 10.2$, 6.6 Hz,

1-H, 3-H, (βMe)*Phe*], 3.67 [dd, J=8.4, 7.2 Hz, 1H, 5-H_b, (*4-Pe*)*Pro*], 3.86 [ddd, J=7.2, 3.0, 3.0 Hz, 1H, 2′-H, (*3-Ncp*)*Ala*], 4.04 (t, J=7.8 Hz, 1H, 1-H, *DCPM*), 4.23–4.31 [m, 3H, C-2, (*4-Pe*)*Pro*, (βMe)*Phe*, *Dap*], 4.32 (ddd, J=13.8, 2.8, 2.8 Hz, 1H, 3-H_b, *Dap*), 4.37 (dd, J=9.0, 4.2 Hz, 1H, 2-H, *Ile*), 4.53 [ddd, J=10.8, 6.0, 6.0 Hz, 1H, 2-H, (*3-Ncp*)*Ala*], 4.58 [dd, J=10.2, 10.2 Hz, 1H, 2-H, (βMe)*Phe*], 5.00 (d, J=12.3 Hz, Bzl-H_a), 5.08 (d, J=12.3 Hz, Bzl-H_b), 5.26–5.33 [m, 1H, 1′-H, (*4-Pe*)*Pro*], 5.56 [dq, J=10.2, 6.6 Hz, 1H, 2′-H, (*4-Pe*)*Pro*], 6.59 (d, J=6.0 Hz, 1H, NH), 6.83 (d, J=9.0 Hz, 1H, NH), 6.2 (d, J=9.6 Hz, 1H, NH), 7.12 (d, J=8.4 Hz, 2H, Ar-H, *MeZ*), 7.16–7.20 (m, 2H, Ar-H), 7.21–7.27 (m, 7H, Ar-H), 7.28–7.37 (m, 3H, Ar-H), 7.50 (d, J=9.0 Hz, 1H, NH), 7.78 (dd, J=10.2, 2.4 Hz, 1H, NH), 8.20 (d, J=6.0 Hz, 1H, NH); the signal of C(CH_3) overlapped the signals of 4-H_b of the *Ile* moiety, 4-H of (βMe)*Phe* residue and 3-H_b of the (*3-Ncp*)*Ala* fragment; ^{13}C NMR (150.8 MHz, $CDCl_3$): δ= 2.6, 2.87, 2.96, 3.0 (−, C-2′, *DCPM*), 11.7 (+, C-5, *Ile*), 13.2 [+, C-3′, (*4-Pe*)*Pro*], 14.2, 14.6 (+, C-1′, *DCPM*), 15.6 (+, C-1′, *Ile*), 18.4 [−, C-3′, (*3-Ncp*)*Ala*], 18.8 [+, C-4, (βMe)*Phe*], 19.8 [+, C-4, (βMe)*Phe*], 21.1 (+, C-1′, *MeZ*), 21.8 [+, C-1′, (*3-Ncp*)*Ala*], 25.2 (−, C-4, *Ile*), 28.3 [+, C-(CH_3)$_3$], 31.1 [−, C-3, (*3-Ncp*)*Ala*], 36.2 [+, C-4, (*4-Pe*)*Pro*], 36.4 [−, C-3, (*4-Pe*)*Pro*], 37.6 (+, C-3, *Ile*), 40.3 [+, C-3, (βMe)*Phe*], 40.8 (−, C-3, *Dap*), 41.7 [+, C-3, (βMe)*Phe*], 51.0 [+, C-2, (*3-Ncp*)*Ala*], 52.4 [−, C-5, (*4-Pe*)*Pro*], 56.5 (+, C-2, *Ile*), 59.2 (+, C-2, *Dap*), 59.5 [+, C-2′, (*3-Ncp*)*Ala*], 60.7 [+, C-2, (*4-Pe*)*Pro*], 61.0 [+, C-2, (βMe)*Phe*], 63.4 [+, C-2, (βMe)*Phe*], 66.7 (−, Bzl-C), 80.2 [C_{quat}, C(CH_3)$_3$], 83.5 (+, C-1, *DCPM*), 126.7 [+, C-2′, (*4-Pe*)*Pro*], 127.0, 127.4, 127.6, 127.7, 128.47, 128.50, 128.93 (? 2) (+, Ar-C), 129.3 [+, C-1′, (*4-Pe*)*Pro*], 133.4, 137.7, 141.8, 141.9 (C_{quat}, Ar-C), 154.4, 156.1 (C_{quat}, NCO_2), 169.7, 170.8, 173.1, 173.4, 174.7, 175.4 (C_{quat}, C-1); IR (KBr): $\tilde{\nu}$=3089, 3062, 3010, 2972, 2933, 2877, 1725, 1667, 1542, 1454, 1416, 1392, 1368, 1258, 1216, 1162 cm^{-1}; MS (ESI): pos.: *m/z* (%): 1197 (100) [M+Na^+]; neg.: *m/z* (%): 1173 (100) [M−H^-]; elemental analysis calcd (%) for $C_{64}H_{86}N_8O_{13}$ (1175.4): C 65.40, H 7.37, N 9.53; found C 65.17, H 7.13, N 9.34.

MeZ-Protected branched cyclohexapeptide (19a) and its epimer (*epi*-19a): The branched hexapeptide **18a** (0.188 g, 0.165 mmol) was deprotected according to GP 5 by treatment with the freshly prepared 2 M HCl in EtOAc (3 mL) to give the hydrochloride of the deprotected peptide as a colorless solid [0.145 g; MS (ESI): pos.: *m/z* (%): 996 (100) [M+H^+]; neg.: *m/z* (%): 994 (100) [M−H^-], which was taken up with anhydrous CH_2Cl_2 (1.5 L) and cyclized by treatment with HATU (2×61 mg, 2×0.160 mmol) and HOAt (2×18 mg, 2×0.133 mmol) and solution of DIEA (2×55 mg, 2×0.426 mmol) in CH_2Cl_2 (2×20 mL) according to GP 2 for 18 h. After this, the solvent was removed under reduced pressure, the residue was taken up with Et_2O (50 mL), and after the usual aqueous work-up (GP 5), drying and filtration, the organic layer was concentrated under reduced pressure. The residue was purified first by column chromatography (acetone/hexane 1:1.75, R_f=0.29), and then by recrystallization (Et_2O/pentane) to give a crude product (81.0 mg), which contained two components according to analytical HPLC. The mixture was separated by preparative HPLC to give cyclodepsipeptide **19a** (41 mg, 28% over two steps) and its epimer *epi*-**19a** (28 mg, 19% over two steps) as colorless solids. Preparative HPLC: column A, isocratic, 85% MeCN in H_2O (0.07% TFA), flow rate 2.5 mL min^{-1}.

Compound 19a: analytical HPLC: isocratic, 60% MeCN in H_2O (0.1% TFA), flow rate=0.5 mL min^{-1}, t_R=20.18 min, purity > 99%; $[\alpha]_D^{20}$=8.6 (c=0.21, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ=0.15–0.31 [m, 1H, 3′-H_a, (*3-Ncp*)*Ala*], 0.32–0.47 [m, 1H, 3-H_a, (*3-Ncp*)*Ala*], 0.78 (t, J=7.2 Hz, 3H, 5-H, *Ile*), 0.84 (d, J=6.6 Hz, 3H, 1′-H, *Ile*), 0.88–0.97 [m, 1H, 1′-H, (*3-Ncp*)*Ala*], 0.97–1.06 (m, 1H, 4-H_a, *Ile*), 1.08–1.25 [m, 1H, 3-H_b, (*3-Ncp*)*Ala*], 1.25 [d, J=7.2 Hz, 3H, 4-H, (βMe)*Phe*], 1.26–1.34 (m, 1H, 4-H_b, *Ile*), 1.29 [d, J=7.2 Hz, 3H, 4-H, (βMe)*Phe*], 1.34–1.44 [m, 1H, 3′-H_b, (*3-Ncp*)*Ala*], 1.40 (d, J=7.2 Hz, 3H, 4-H, *a-Dab*), 1.63–1.73 (m, 1H, 3-H, *Ile*), 1.66 [d, J=6.6 Hz, 3′-H, (*4-Pe*)*Pro*], 1.87 [ddd, J=11.4, 11.4, 11.4 Hz, 1H, 3-H_a, (*4-Pe*)*Pro*], 2.18 [ddd, J=11.4, 6.0, 6.0 Hz, 1H, 3-H_b, (*4-Pe*)*Pro*], 2.38 (s, 3H, 1′-H, *MeZ*), 3.01 [dddd, J=1.2, 7.2 Hz, 1H, 3-H, (βMe)*Phe*], 3.07–3.19 [m, 1H, 4-H, (*4-Pe*)*Pro*], 3.23 [dd, J=9.8, 9.8 Hz, 1H, 5-H_a, (*4-Pe*)*Pro*], 3.40–3.51 [m, 1H, 2′-H, (*3-Ncp*)*Ala*], 3.64–3.71 [m, 1H, 3-H, (βMe)*Phe*], 3.71–3.79 [m, 1H, 2-H, (*3-Ncp*)*Ala*], 3.78–3.85 [m, 1H, 2-H, (*4-Pe*)*Pro*], 3.86–3.94 [m, 1H, 5-H_b, (*4-Pe*)*Pro*], 4.28–4.34 [m, 2H, 3-H, *a-Dab*, 2-H, (βMe)*Phe*], 4.34–4.50 (m, 1H, 2-H, *a-Dab*), 4.50–4.60 [m, 2H, 2-H, *Ile*, 2-H, (βMe)*Phe*], 4.97 (d, J=12.0 Hz, Bzl-H_a), 5.19 (d, J=12.0 Hz, Bzl-H_b), 5.25 [dd, J=9.6, 9.6 Hz, 1H, 1′-H, (*4-Pe*)*Pro*], 5.58 [dq, J=9.6, 7.2 Hz, 1H, 2′-H, (*4-Pe*)*Pro*], 5.63–5.80 (br, 1H, NH), 6.04–6.37 (br, 1H, NH), 6.51–6.67 (br, 1H, NH), 6.86–7.02 (br, 1H, NH), 7.02–7.12 (m, 1H, NH), 7.14–7.31 (m, 15H, Ar-H, NH); ^{13}C NMR (150.8 MHz, $CDCl_3$): δ=10.5 (+, C-5, *Ile*), 13.2 [+, C-3′, (*4-Pe*)*Pro*], 13.5 [+, C-4, (βMe)*Phe*], 14.9 (+, C-1′, *Ile*), 17.8 [−, C-3′, (*3-Ncp*)*Ala*], 18.0 [+, C-4, (βMe)*Phe*], 18.7 (+, C-4, *a-Dab*), 21.0 [+, C-1′, (*3-Ncp*)*Ala*], 21.1 (+, C-1′, *MeZ*), 24.3 (−, C-4, *Ile*), 32.7 [−, C-3, (*3-Ncp*)*Ala*], 35.2 [−, C-3, (*4-Pe*)*Pro*], 36.6 [+, C-4, (*4-Pe*)*Pro*], 37.3 (+, C-3, *Ile*), 38.8 [+, C-3, (βMe)*Phe*], 43.6 [+, C-3, (βMe)*Phe*], 47.5 (+, C-3, *a-Dab*), 52.5 [+, C-2, (*3-Ncp*)*Ala*], 52.7 [−, C-5, (*4-Pe*)*Pro*], 54.5 (+, C-2, *Ile*), 58.9 [+, C-2′, (*3-Ncp*)*Ala*], 59.30 [+, 2 ? C-2, *a-Dab*, (βMe)*Phe*], 59.5 [+, C-2, (βMe)*Phe*], 62.3 [+, C-2, (*4-Pe*)*Pro*], 67.0 (−, Bzl-C), 126.8, 127.1, 127.2, 127.5 (+, Ar-C), 127.7 [C-2′, (*4-Pe*)*Pro*], 128.0 (+, Ar-C), 128.4 [C-1′, (*4-Pe*)*Pro*], 128.5, 128.6, 129.1 (+, Ar-C), 133.4, 137.8, 141.4, 142.3 (C_{quat}, Ar-C), 157.3 (C_{quat}, NCO_2), 169.1, 170.49 (× 2), 170.90 (× 2), 172.0 (C_{quat}, C-1); IR (KBr): $\tilde{\nu}$=3060, 3029, 2969, 2936, 2877, 1670, 1634, 1542, 1517, 1452, 1369, 1205 cm^{-1}; MS (ESI): pos.: *m/z* (%): 1000 (100) [M+Na^+]; neg.: *m/z* (%): 976 (100) [M−H^-]; HRMS (ESI): *m/z*: calcd for [$C_{53}H_{68}N_8O_{10}Na^+$]: 999.4951; found 999.4951.

***epi*-19a**: analytical HPLC 1: isocratic, 60% MeCN in H_2O (0.1% TFA), flow rate=0.5 mL min^{-1}, t_R=17.25 min, purity > 97%; $[\alpha]_D^{20}$=−42.68 (c=0.27, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ=0.65–0.73 (m, 3H, 1′-H, *a-Ile*), 0.84 (t, J=7.2 Hz, 3H, 5-H, *a-Ile*), 0.89 [ddd, J=5.4, 5.4, 5.4 Hz, 1H, 3′-H_a, (*3-Ncp*)*Ala*], 1.10 [d, J=5.4 Hz, 3H, 4-H, (βMe)*Phe*], 1.10–1.15 [m, 1H, 3-H_a*, (*3-Ncp*)*Ala*], 1.17–1.26 [m, 4H, 4-H, (βMe)*Phe*, 4-H_a*, *a-Ile*], 1.40–1.48 [m, 1H, 3-H_b*, (*3-Ncp*)*Ala*], 1.44 (d, J=7.8 Hz, 3H, 4-H, *a-Dab*), 1.50–1.59 [m, 1H, 1′-H, (*3-Ncp*)*Ala*], 1.59–1.63 [m, 2H, 3′-H_b, (*3-Ncp*)*Ala*, 3-H, *a-Ile*], 1.63 [d, J=6.6 Hz, 3′-H, (*4-Pe*)*Pro*], 2.08–2.22 [m, 1H, 3-H_a, (*4-Pe*)*Pro*], 2.28 (s, 3H, 1′-H, *MeZ*), 2.25–2.33 [m, 1H, 3-H_b, (*4-Pe*)*Pro*], 3.06 [ddddd, J=7.8, 7.8, 7.8, 7.8, 7.8 Hz, 1H, 4-H, (*4-Pe*)*Pro*], 3.17–3.30 [m, 2H, 5-H_a, (*4-Pe*)*Pro*, 3-H*, (βMe)*Phe*], 3.31–3.44 [m, 2H, 2′-H*, (*3-Ncp*)*Ala*, 3-H, (βMe)*Phe*], 3.74 [dd, J=7.8, 7.8 Hz, 1H, 5-H_b, (*4-Pe*)*Pro*], 3.74–3.84 (m, 1H, 2-H), 4.08–4.20 (m, 1H, 3-H, *a-Dab*), 4.31–4.84 (m, 2H, 2-H), 4.48–4.62 (m, 2H, 2-H), 4.73 (dd, J=7.8, 7.8 Hz, 1H, 2-H), 4.98 (d, J=12.0 Hz, Bzl-H_a), 5.09 (d, J=12.0 Hz, Bzl-H_b), 5.29 [dd, J=10.2, 10.2 Hz, 1H, 1′-H, (*4-Pe*)*Pro*], 5.52 [dq, J=10.2, 6.6 Hz, 1H, 2′-H, (*4-Pe*)*Pro*], 5.92–6.04 (br, 1H, NH), 6.74 (d, J=7.2 Hz, 1H, NH), 7.05–7.12 (br, 1H, NH), 7.07 (d, J=7.8 Hz, 2H, Ar-H), 7.16–7.29 (m, 10H, Ar-H, NH), 7.30–7.36 (m, 4H, Ar-H, NH), 7.44–7.51 (br, 1H, NH); the absorption of 4-H_b, *a-Ile* is masked by the signal of 3′-H, (*4-Pe*)*Pro*; ^{13}C NMR (150.8 MHz, $CDCl_3$): δ=11.7 (+, C-5, *a-Ile*), 13.2 [+, C-3′, (*4-Pe*)*Pro*], 14.0 (+, C-1′, *a-Ile*), 17.3 [+, C-4, (βMe)*Phe*], 17.5 (+, C-4, *a-Dab*), 17.6 [−, C-3′, (*3-Ncp*)*Ala*], 17.6 [+, C-4, (βMe)*Phe*], 21.1 (+, C-1′, *MeZ*), 21.9 [+, C-1′, (*3-Ncp*)*Ala*], 26.3 (−, C-4, *a-Ile*), 31.8 [−, C-3, (*3-Ncp*)*Ala*], 34.2 [−, C-3, (*4-Pe*)*Pro*], 36.1 [+, C-4, (*4-Pe*)*Pro*], 36.9 (+, C-3, *a-Ile*), 40.43 [+, 2×C-3, (βMe)*Phe*], 49.3 (+, C-3, *a-Dab*), 51.0 (+, C-2), 52.9 [−, C-5, (*4-Pe*)*Pro*], 54.1 (+, C-2), 58.8 [+, C-2′*, (*3-Ncp*)*Ala*], 59.3 (+, C-2*), 59.4 (+, C-2*), 60.34 (+, 2×C-2), 67.2 (−, Bzl-C), 126.7, 127.0, 127.6, 127.7, 128.2, 128.3, 128.5, 128.7, 129.0, 129.1 [+, Ar-C, C-1′, C-2′, (*4-Pe*)*Pro*], 132.8, 138.0, 142.0, 142.6 (C_{quat}, Ar-C), 156.2 (C_{quat}, NCO_2), 170.33 (× 2), 170.82 (× 2), 170.9, 171.0 (C_{quat}, C-1); IR (KBr): $\tilde{\nu}$= 3061, 3030, 2969, 2934, 2877, 1654, 1540, 1453, 1369, 1270 cm^{-1}; MS (ESI): pos.: *m/z* (%): 1000 (100) [M+Na^+]; neg.: *m/z* (%): 976 (100) [M−H^-].

MeZ-*a*-N$_\beta$Me-Dab[Boc-(4-Pe)Pro]-(βMe)Phe-(*R*)-(3-Ncp)Ala-(βMe)Phe-Ile-OH: $(Bu)_4N^-F^+$ (70.0 mg, 0.22 mmol) was added to a stirred solution of the ester **18b** (88.0 mg, 72.8 μmol) in MeCN (2.0 mL), and the mixture was stirred at 20 °C for an additional 1 h. As TLC showed the presence of the starting material the mixture was carefully heated at 55 °C with a heat-gun and then was stirred for another 1 h. 1 N H_2SO_4 (1 mL) was added, and the reaction mixture was then diluted with Et_2O (40 mL), washed with 1 M $KHSO_4$ (3×10 mL), water (3×10 mL), brine (2×10 mL), dried, filtered and concentrated under reduced pressure. The residue was recrystallized from Et_2O/pentane to give the title compound (79.0 mg, 98%) as a colorless solid which was used for the next step without additional purification. R_f=0.36, acetone/hexane 4:7

(3% AcOH); MS (ESI): pos.: *m/z* (%): 1153 (78) [*M*−H+2Na$^+$], 1131 (100) [*M*+Na$^+$]; neg.: *m/z* (%): 1107 (100) [*M*−H$^-$].

MeZ-Protected branched cyclohexapeptide (19b): The branched hexapeptide acid MeZ-*a*-N$_\beta$Me-Dab[Boc-(4-Pe)Pro]-(βMe)Phe-(*R*)-(3-Ncp)Ala-(βMe)Phe-Ile-OH (79.0 mg, 71.2 μmol) was deprotected according to GP 5 by treatment with 2 M HCl in EtOAc (2 mL) to give the hydrochloride of the deprotected material as a colorless solid (80 mg), which was taken up with anhydrous CH_2Cl_2 (1.1 L) and cyclized by treatment with HATU (2×28.0 mg, 2×73.3 μmol) and HOAt (2×9.6 mg, 2×73.3 μmol) and solution of DIEA (2×37 mg, 2×0.285 mmol) in CH_2Cl_2 (2×50 mL) according to GP 2 for 22 h. After this, the solvent was removed under reduced pressure, the residue was taken up with Et_2O (50 mL), and after the usual aqueous work-up (GP 5), drying and filtration, the organic layer was concentrated under reduced pressure. The residue was purified first by column chromatography (acetone/hexane 1:2, R_f=0.32) to give a crude product (43.0 mg), which was finally purified by preparative HPLC to give cyclodepsipeptide **19b** (31.6 mg, 44% over three steps) and a small amount of its epimer *epi*-**19b** (1.4 mg, 2% over three steps) as colorless solids. Preparative HPLC: column B, isocratic, 65% MeCN in H_2O (0.1% TFA), flow rate 2.7 mL min^{-1}.

Compound 19b: analytical HPLC: isocratic, 75% MeCN in H_2O (0.1% TFA), flow rate = 0.5 mL min^{-1}, t_R = 10.64 min, purity > 99%; gradient 55 → 100% MeCN in H_2O (0.1% TFA) for 15 min, flow rate = 0.5 mL min^{-1}, t_R = 14.65 min, purity > 99%; $[\alpha]_D^{20}$ = 37.8 (*c* = 0.33, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.69–0.77 [m, 1H, 3-H$_a$, (*3-Ncp*)*Ala*], 0.77 (t, *J* = 7.2 Hz, 3H, 5-H, *Ile*), 0.79 (d, *J* = 7.2 Hz, 3H, 1′-H, *Ile*), 0.85 [ddd, *J* = 7.2, 7.2, 7.2 Hz, 1H, 3′-H$_a$, (*3-Ncp*)*Ala*], 1.11 (ddq, *J* = 7.8, 6.6, 6.6 Hz, 1H, 4-H$_a$, *Ile*), 1.34 [d, *J* = 6.6 Hz, 3H, 4-H, (β*Me*)*Phe*], 1.32–1.41 [m, 2H, 4-H$_b$, *Ile*, 1′-H, (*3-Ncp*)*Ala*], 1.42 [d, *J* = 6.6 Hz, 3H, 4-H, (β*Me*)*Phe*], 1.34–1.44 [m, 1H, 3′-H$_b$, (*3-Ncp*)*Ala*], 1.58 (d, *J* = 7.2 Hz, 3H, 4-H, *a*-N$_\beta$*Me-Dab*), 1.59–1.64 [m, 3H, 3-H, *Ile*, 3-H$_b$, 3′-H$_b$, (*3-Ncp*)*Ala*], 1.66 [dd, *J* = 7.2, 1.8 Hz, 3′-H, (*4-Pe*)*Pro*], 1.73 [ddd, *J* = 12.0, 12.0, 12.0 Hz, 1H, 3-H$_a$, (*4-Pe*)*Pro*], 2.13 [ddd, *J* = 12.0, 6.0, 6.0 Hz, 1H, 3-H$_b$, (*4-Pe*)*Pro*], 2.35 (s, 3H, 1′-H, *MeZ*), 2.92 (s, 3H, NMe, *a*-N$_\beta$*Me-Dab*), 2.99 [dq, *J* = 6.6, 7.5 Hz, 1H, 3-H, (β*Me*)*Phe*], 3.17–3.30 [m, 2H, 4-H, 5-H$_a$, (*4-Pe*)*Pro*], 3.48 [dq, *J* = 6.6, 6.6 Hz, 1H, 3-H, (β*Me*)*Phe*], 3.62–3.72 [m, 1H, 2-H, (*3-Ncp*)*Ala*], 3.84 [ddd, *J* = 7.2, 3.0, 3.0 Hz, 1H, 2′-H, (*3-Ncp*)*Ala*], 4.01–4.10 [m, 1H, 5-H$_b$, (*4-Pe*)*Pro*], 4.29 (d, *J* = 7.2 Hz, 1H, 2-H, *a*-N$_\beta$*Me-Dab*), 4.45 [dd, *J* = 10.2, 6.6 Hz, 1H, 2-H, (β*Me*)*Phe*], 4.45–4.54 [m, 2H, 2-H, *Ile*, 2-H, (*4-Pe*)*Pro*], 4.34–4.50 (m, 1H, 2-H, *a-Dab*), 4.71 [dd, *J* = 7.5, 7.5 Hz, 1H, 2-H, (β*Me*)*Phe*], 4.99 (dd, *J* = 7.2, 7.2 Hz, 3-H, *a*-N$_\beta$*Me-Dab*), 5.09 (s, 2H, Bzl), 5.17–5.27 [dd, *J* = 9.6, 9.6 Hz, 1H, 1′-H, (*4-Pe*)*Pro*], 5.57 [dq, *J* = 9.6, 7.2 Hz, 1H, 2′-H, (*4-Pe*)*Pro*], 6.11 (d, *J* = 6.0 Hz, 1H, NH), 6.23–6.37 (br, 2H, 2×NH), 6.51–6.67 (br, 1H, NH), 7.01 (d, *J* = 6.0 Hz, 1H, NH), 7.09–7.21 (m, 6H, Ar-H), 7.22–7.27 (m, 4H, Ar-H), 7.28 (dd, *J* = 7.2 Hz, Ar-H), 7.35 (dd, *J* = 7.8, 7.8 Hz, Ar-H), 7.43 (d, *J* = 8.4 Hz, NH); ^{13}C NMR (150.8 MHz, $CDCl_3$): δ = 10.1 (+, C-5, *Ile*), 13.4 [+, C-3′, (*4-Pe*)*Pro*], 14.7 (+, C-1′, *Ile*), 15.3 [+, C-4, (β*Me*)*Phe*], 17.04 (+, C-4, *a*-N$_\beta$*Me-Dab*), 17.2 [−, C-3′, (*3-Ncp*)*Ala*], 18.2 [+, C-4, (β*Me*)*Phe*], 21.2 (+, C-1′, *MeZ*), 21.4 [+, C-1′, (*3-Ncp*)*Ala*], 24.7 (−, C-4, *Ile*), 31.2 (+, NMe, *a*-N$_\beta$*Me-Dab*), 32.2 [−, C-3, (*3-Ncp*)*Ala*], 35.0 [−, C-3, (*4-Pe*)*Pro*], 36.3 (+, C-3, *Ile*), 36.9 [+, C-4, (*4-Pe*)*Pro*], 39.6 [+, C-3, (β*Me*)*Phe*], 45.5 [+, C-3, (β*Me*)*Phe*], 52.0 (+, C-3, *a*-N$_\beta$*Me-Dab*), 52.6 [−, C-5, (*4-Pe*)*Pro*], 53.8 [+, C-2, (*3-Ncp*)*Ala*], 54.6 (+, C-2, *Ile*), 57.5 [+, C-2, (β*Me*)*Phe*], 58.9 [+, C-2, (β*Me*)*Phe*], 59.0 [+, C-2′, (*3-Ncp*)*Ala*], 60.3 [+, C-2, (*4-Pe*)*Pro*], 61.6 (+, C-2, *a*-N$_\beta$*Me-Dab*), 67.0 (−, Bzl-C), 127.1, 127.3, 127.57, 127.62 (+, Ar-C), 127.7 [+, C-2′, (*4-Pe*)*Pro*], 128.1 [+, C-1′, (*4-Pe*)*Pro*], 128.3, 128.6, 128.8, 129.1 (+, Ar-C), 133.3, 137.9, 140.8, 142.5 (C_{quat}, Ar-C), 156.6 (C_{quat}, NCO_2), 170.2, 170.4, 170.7, 170.8, 171.0, 174.8 (C_{quat}, C-1); IR (KBr): $\tilde{\nu}$ = 2971, 2936, 2878, 1720, 1633, 1541, 1506, 1453, 1369, 1209, 1032 cm^{-1}; MS (ESI): pos.: *m/z* (%): 1013 (100) [*M*+Na$^+$]; neg.: *m/z* (%): 989 (100) [*M*−H$^-$]; HRMS (ESI): *m/z*: calcd for [$C_{54}H_{71}N_8O_{10}^+$]: 991.5288; found 991.5291.

***epi*-19b**: analytical HPLC: isocratic, 75% MeCN in H_2O (0.1% TFA), flow rate = 0.5 mL min^{-1}, t_R = 9.61 min, purity > 95%; gradient 55 → 100% MeCN in H_2O (0.1% TFA) for 15 min, flow rate = 0.5 mL min^{-1}, t_R = 14.15 min, purity > 95%; MS (ESI): pos.: *m/z* (%): 1013 (100) [*M*+Na$^+$]; neg.: *m/z* (%): 989 (100) [*M*−H$^-$].

MeZ-Protected branched cyclohexapeptide (19c) and its epimer (*epi*-19c): The branched hexapeptide **18c** (0.134 g, 0.114 mmol) was deprotected according to GP 5 by treatment with a freshly prepared 2 M HCl in EtOAc (2.5 mL) to give the hydrochloride of the deprotected peptide as a colorless solid, which was taken up with anhydrous CH_2Cl_2 (1.3 L) and cyclized by treatment with HATU (2×44.6 mg, 2×0.117 mmol), HOAt (2×15.9 mg, 2×0.117 mmol) and a solution of DIEA (2×59 mg, 2×0.456 mmol) in CH_2Cl_2 (2×50 mL) according to GP 2 for 18 h. After this, the solvent was removed under reduced pressure, the residue was taken up with Et_2O (50 mL), and after the usual aqueous work-up (GP 5), drying and filtration, the organic layer was concentrated under reduced pressure. The residue was purified by column chromatography (acetone/hexane 1:1.5, R_f=0.31) to give a crude product (90.0 mg), which contained two components according to analytical HPLC. The mixture was separated by preparative HPLC to give cyclodepsipeptide **19c** (37.7 mg, 34% over two steps) and its epimer *epi*-**19a** (27.9 mg, 25% over two steps) as colorless solids. Preparative HPLC: column B, isocratic, 69% MeCN in H_2O (0.1% TFA), flow rate 2.5 mL min^{-1}.

Compound 19c: analytical HPLC: isocratic, 70% MeCN in H_2O (0.1% TFA), flow rate = 0.5 mL min^{-1}, t_R = 12.00 min, purity > 99%; $[\alpha]_D^{20}$ = 16.0 (*c* = 0.77, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.40–0.54 [m, 1H, 3-H$_a$, (*3-Ncp*)*Ala*], 0.58–0.69 [m, 1H, 3′-H$_a$, (*3-Ncp*)*Ala*], 0.76 (t, *J* = 7.2 Hz, 3H, 5-H, *Ile*), 0.88 (d, *J* = 6.0 Hz, 3H, 1′-H, *Ile*), 1.00–1.17 [m, 2H, 1′-H, (*3-Ncp*)*Ala*, 1H, 4-H$_a$, *Ile*], 1.26 [d, *J* = 6.6 Hz, 3H, 4-H, (β*Me*)*Phe*], 1.26–1.34 [m, 1H, 3-H$_b$, (*3-Ncp*)*Ala*], 1.34 [d, *J* = 7.2 Hz, 3H, 4-H, (β*Me*)*Phe*], 1.42–1.49 [m, 1H, 3′-H$_b$, (*3-Ncp*)*Ala*], 1.59 [d, *J* = 6.6 Hz, 3′-H, (*4-Pe*)*Pro*], 1.69–1.79 (m, 1H, 3-H, *Ile*), 1.81 [ddd, *J* = 12.0, 12.0, 12.0 Hz, 1H, 3-H$_a$, (*4-Pe*)*Pro*], 2.16 [ddd, *J* = 12.0, 6.0, 6.0 Hz, 1H, 3-H$_b$, (*4-Pe*)*Pro*], 2.35 (s, 3H, 1′-H, *MeZ*), 2.90 [dq, *J* = 6.0, 6.0 Hz, 1H, 3-H, (β*Me*)*Phe*], 3.03–3.15 [m, 1H, 4-H, (*4-Pe*)*Pro*], 3.23 [dd, *J* = 9.2, 9.2 Hz, 1H, 5-H$_a$, (*4-Pe*)*Pro*], 3.43–3.58 [m, 2H, 2-H, (*3-Ncp*)*Ala*, 3-H$_a$, *Dap*], 3.62–3.72 [m, 2H, 3-H, (β*Me*)*Phe*, 2′-H, (*3-Ncp*)*Ala*], 3.84–3.93 [m, 1H, 3-H$_b$, *Dap*], 3.94 [dd, *J* = 9.2, 9.2 Hz, 1H, 5-H$_b$, (*4-Pe*)*Pro*], 4.03–4.12 [m, 1H, 2-H, (*4-Pe*)*Pro*], 4.41–4.48 (m, 1H, *Dap*), 4.50–4.55 [m, 1H, 2-H, (β*Me*)*Phe*], 4.59 (dd, *J* = 8.7, 8.7 Hz, 1H, 2-H, *Ile*), 4.64 [dd, *J* = 7.8, 7.8 Hz, 1H, 2-H, (β*Me*)*Phe*], 5.06 (d, *J* = 12.0 Hz, Bzl-H$_a$), 5.13 (d, *J* = 12.0 Hz, Bzl-H$_b$), 5.22 [dd, *J* = 10.2, 10.2 Hz, 1H, 1′-H, (*4-Pe*)*Pro*], 5.57 [dq, *J* = 10.2, 6.6 Hz, 1H, 2′-H, (*4-Pe*)*Pro*], 6.06–6.23 (br, 1H, NH), 6.71–6.90 (br, 2H, 2×NH), 6.98–7.09 (br, 1H, NH), 7.11–7.18 (m, 3H, Ar-H), 7.18–7.22 (m, 2H, Ar-H), 7.22–7.28 (m, 7H, Ar-H), 7.28–7.34 (m, 2H, Ar-H), 7.34–7.57 (br, 1H, NH), 7.59–7.84 (br, 1H, NH); the signal of 4-H of the (β*Me*)*Phe* residue (1.34 ppm) overlapped the signal of 4-H$_b$ of the *Ile* moiety; ^{13}C NMR (150.8 MHz, $CDCl_3$): δ = 10.6 (+, C-5, *Ile*), 13.3 [+, C-3′, (*4-Pe*)*Pro*], 13.9 [+, C-4, (β*Me*)*Phe*], 15.0 (+, C-1′, *Ile*), 17.3 [−, C-3′, (*3-Ncp*)*Ala*], 17.9 [+, C-4, (β*Me*)*Phe*], 21.25 (+, C-1′, *MeZ*), 21.33 [+, C-1′, (*3-Ncp*)*Ala*], 24.6 (−, C-4, *Ile*), 32.0 [−, C-3, (*3-Ncp*)*Ala*], 35.2 [−, C-3, (*4-Pe*)*Pro*], 36.9 [+, C-4, (*4-Pe*)*Pro*], 37.3 (+, C-3, *Ile*), 39.1 [+, C-3, (β*Me*)*Phe*], 40.6 (−, C-3, *Dap*), 45.0 [+, C-3, (β*Me*)*Phe*], 53.0 [−, C-5, (*4-Pe*)*Pro*], 53.7 [+, C-2, (*3-Ncp*)*Ala*], 54.6 (+, C-2, *Ile*), 57.8 (+, C-2, *Dap*), 58.8 [+, C-2, (β*Me*)*Phe*], 59.1 [+, C-2′, (*3-Ncp*)*Ala*], 59.5 [+, C-2, (β*Me*)*Phe*], 61.5 [+, C-2, (*4-Pe*)*Pro*], 67.2 (−, Bzl-C), 127.08, 127.12, 127.4, 127.7 [C-2′, (*4-Pe*)*Pro*], 128.0 [C-1′, (*4-Pe*)*Pro*], 128.3, 128.6, 128.8, 129.17 (×2) (+, Ar-C), 133.3, 137.9, 141.3, 142.1 (C_{quat}, Ar-C), 157.3 (C_{quat}, NCO_2), 169.2, 170.9 (×2), 171.4, 172.0, 174.2 (C_{quat}, C-1); IR (KBr): $\tilde{\nu}$ = 3060, 3029, 2972, 2936, 2879, 1725, 1667, 1638, 1543, 1513, 1453, 1369, 1204 cm^{-1}; MS (ESI): pos.: *m/z* (%): 986 (100) [*M*+Na$^+$]; neg.: *m/z* (%): 962 (100) [*M*−H$^-$]; HRMS (ESI): *m/z*: calcd for [$C_{52}H_{66}N_8O_{10}Na^+$]: 985.4794; found 985.4797.

***epi*-19c**: analytical HPLC 1: isocratic, 60% MeCN in H_2O (0.1% TFA), flow rate = 0.5 mL min^{-1}, t_R = 9.44 min, purity > 99%; $[\alpha]_D^{20}$ = −43.1 (*c* = 0.42, $CHCl_3$); ^{1}H NMR (600 MHz, $C_2D_2Cl_4$, 353.1 K): δ = 0.67 (d, *J* = 6.0 Hz, 3H, 1′-H, *a-Ile*), 0.82 (t, *J* = 7.2 Hz, 3H, 5-H, *a-Ile*), 0.93 [ddd, *J* = 6.6, 6.6, 6.6 Hz, 1H, 3′-H$_a$, (*3-Ncp*)*Ala*], 0.93–0.99 (m, 1H, 4-H$_a$, *a-Ile*), 1.05–1.15 (m, 1H, 4-H$_b$, *a-Ile*), 1.24 [d, *J* = 6.6 Hz, 3H, 4-H, (β*Me*)*Phe*], 1.37 [d, *J* = 6.6 Hz, 3H, 4-H, (β*Me*)*Phe*], 1.37–1.45 [m, 1H, 3-H$_a$, (*3-Ncp*)*Ala*], 1.54–1.63 [m, 2H, 3-H$_b$, (*3-Ncp*)*Ala*, 3-H, *a-Ile*], 1.66 [d, *J* = 6.0 Hz, 3′-H, (*4-Pe*)*Pro*], 1.67–1.76 [m, 1H, 1′-H, (*3-Ncp*)*Ala*], 1.84 [ddd, *J* = 10.2, 10.2, 10.2 Hz, 1H, 3-H$_a$, (*4-Pe*)*Pro*], 2.34 (s, 3H, 1′-H, *MeZ*), 2.35–2.44 [m, 1H, 3-H$_b$, (*4-Pe*)*Pro*], 3.07 [m, 1H, 4-H, (*4-Pe*)*Pro*], 3.27

[dd, $J=9.2$, 9.2 Hz, 1H, 5-H_a, (*4-Pe*)*Pro*], 3.31–3.40 [m, 2H, 2 ? 3-H, (β*Me*)*Phe*], 3.48–3.66 (m, 1H, 3-H, *Dap*), 3.74 [dd, $J=9.2$, 9.2 Hz, 1H, 5-H_b, (*4-Pe*)*Pro*], 3.85–3.92 [m, 1H, 2′-H, (*3-Ncp*)*Ala*], 4.29–4.40 [m, 3H, 2-H, *a-Ile*, 2 ? 2-H, (β*Me*)*Phe*], 4.41–4.47 [m, 1H, 2-H, (*3-Ncp*)*Ala*], 4.47–4.54 [m, 1H, 2-H, (*4-Pe*)*Pro*], 4.61 (dd, $J=8.4$, 8.4 Hz, 1H, 2-H, *Dap*), 5.10 (d, $J=12.0$ Hz, Bzl-H_a), 5.14 (d, $J=12.0$ Hz, Bzl-H_b), 5.27–5.35 [dd, $J=10.2$, 10.2 Hz, 1H, 1′-H, (*4-Pe*)*Pro*], 5.61 [dq, $J=10.2$, 6.0 Hz, 1H, 2′-H, (*4-Pe*)*Pro*], 6.55–6.69 (br, 2H, NH), 6.89–7.01 (br, 2H, NH), 7.15 (d, $J=7.2$ Hz, 2H, Ar-H, *MeZ*), 7.18–7.22 (m, 1H, Ar-H), 7.22–7.29 (m, 11H, Ar-H), 7.29–7.36 (m, 3H, Ar-H), 7.39–7.48 (br, 2H, NH); the absorption of 3′-H_b, (*3-Ncp*)*Ala* is masked by the signal of 3′-H, (*4-Pe*)*Pro*; ^{13}C NMR (150.8 MHz, $C_2D_2Cl_4$, 353.1 K): $\delta=11.4$ (+, C-5, *a-Ile*), 12.8 [+, C-3′, (*4-Pe*)*Pro*], 13.6 (+, C-1′, *a-Ile*), 16.9 [+, C-4, (β*Me*)*Phe*], 17.2 [+, C-4, (β*Me*)*Phe*], 17.4 [−, C-3′, (*3-Ncp*)*Ala*], 20.8 (+, C-1′, *MeZ*), 21.9 [+, C-1′, (*3-Ncp*)*Ala*], 26.2 (−, C-4, *a-Ile*), 32.1 [−, C-3, (*3-Ncp*)*Ala*], 35.4 [−, C-3, (*4-Pe*)*Pro*], 36.0 (+, C-3, *a-Ile*), 36.3 [+, C-4, (*4-Pe*)*Pro*], 39.9 [+, C-3, (β*Me*)*Phe*], 41.1 [+, C-3, (β*Me*)*Phe*], 42.4 (−, C-3, *Dap*), 51.5 [+, C-2, (*3-Ncp*)*Ala*], 52.2 [−, C-5, (*4-Pe*)*Pro*], 54.3 (+, C-2, *a-Ile*), 55.8 [+, C-2, (*4-Pe*)*Pro*], 58.8 (+, C-2, *Dap*), 59.3 [+, C-2′, (*3-Ncp*)*Ala*], 60.0 [+, C-2, (β*Me*)*Phe*], 60.4 [+, C-2, (β*Me*)*Phe*], 67.0 (−, Bzl-C), 126.5, 126.8 (+, Ar-C), 127.1 [+, C-2′, (*4-Pe*)*Pro*], 127.4, 127.5, 128.0, 128.3, 128.4 (+, Ar-C), 128.6 [+, C-1′, (*4-Pe*)*Pro*], 129.0 (+, Ar-C), 132.9, 137.8, 142.3, 142.5 (C_{quat}, Ar-C), 156.3 (C_{quat}, NCO_2), 170.2, 170.3, 170.6, 170.8, 171.3, 173.2 (C_{quat}, C-1); IR (KBr): $\tilde{\nu}=3034$, 2969, 2871, 1659, 1541, 1453, 1369, 1256, 1206, 1065 cm^{-1}; MS (ESI): pos.: *m/z* (%): 985 (100) [*M*+Na^+]; neg.: *m/z* (%): 961 (100) [*M*−H^-]; HRMS (ESI): *m/z*: calcd for [$C_{52}H_{66}N_8O_{10}Na^+$]: 985.4794; found 985.4793.

[*a*-Dab^1]-Hormaomycin (2a): A solution of the CHA salt of Teoc-(2*S*,1′*R*,2′*R*)-(3-Ncp)AlaOH (26.6 mg, 63.75 μmol) in Et_2O (50 mL) was washed with 1 M H_2SO_4 (3×5 mL), 1 M $KHSO_4$ (2×5 mL), water (3×5 mL), brine (2×5 mL), dried, filtered and concentrated under reduced pressure. The resulting *N*-protected amino acid was dried at 0.02 Torr for 2 h and then coupled with the depsipeptide, obtained after deprotection of **19a** (19.5 mg, 19.96 μmol) by treatment with 10% anisole in TFA (1.1 mL) according to GP 6 for 2 h, applying HATU (22.8 mg, 59.96 μmol), HOAt (8.1 mg, 59.94 μmol), DIEA (2.57 mg, 19.88 μmol) and TMP (21.8 mg, 179.00 μmol) in CH_2Cl_2 (3 mL) according to GP 4 for 15 h. The mixture was then diluted with Et_2O (40 mL), and the crude product obtained after the usual aqueous work-up (GP 2) was purified by preparative TLC (200×200 mm, acetone/hexane 1:2.7) to give the respective Teoc-(*S*)-(3-Ncp)Ala-cyclohexapeptide (21.6 mg, 96%; $R_f=0.18$, acetone/hexane 1:2.5) as a colorless glass which was used for the next step without any characterization. This substance (21.6 mg, 19.13 μmol) was deprotected by treatment with TFA (2.0 mL) for 1 h. The mixture was concentrated under reduced pressure at 20 °C and then taken up with toluene (3×15 mL), which was distilled off to remove the last traces of TFA. The resulting deprotected branched peptide was coupled with Chpca(MOM)-OH **20** (7.0 mg, 34.04 μmol) by treatment with HATU (12.9 mg, 33.93 μmol), DIEA (2.47 mg, 19.13 μmol) and TMP (12.37 mg, 102.08 μmol) in CH_2Cl_2 (3 mL) according to GP 4 for 5 h. The mixture was then diluted with Et_2O (40 mL) and the crude product obtained after the usual aqueous work-up (GP 2) was purified by preparative TLC (200×200 mm, acetone/hexane 1:2.7, two fold development) and finally by recrystallization from Et_2O/hexane to give the *O*-MOM protected [*a*-Dab^1]-hormaomycin (20.2 mg, 90%; $R_f=0.09$, acetone/hexane 1:3) as a colorless solid which was used for the next step without any characterization. MOM-**2a** (19.1 mg, 16.92 μmol) was deprotected appling $MgBr_2$•Et_2O (164 mg, 633.89 μmol) and EtSH (0.018 mL, 243.07 μmol) in CH_2Cl_2 (10 mL) according to GP 7 for 3 h. The mixture was diluted with Et_2O (50 mL), and the crude product obtained after the usual aqueous work-up (GP 7) was recrystallized from Et_2O/pentane and then from CH_2Cl_2/pentane to give **2a** (15.4 mg, 84%, 68% over five steps from **19a**) as a colorless solid. $R_f=0.14$, acetone/hexane 1:2.5; analytical HPLC: gradient 25 → 85% MeCN in 0.15% ammonium acetate buffer (pH 5.5) for 25 min, flow rate = 0.5 mL min^{-1}, $t_R=21.72$ min, purity > 99%; $[\alpha]_D^{20}=23.0$ ($c=0.1$, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): $\delta=-0.69$ [ddd, $J=6.6$, 6.6, 6.6 Hz, 1H, 3′-H_a, (*3-Ncp*)*Ala*], −0.17–0.07 [m, 1H, 3-H_a, (*3-Ncp*)*Ala*], 0.20–0.27 [m, 1H, 1′-H, (*3-Ncp*)*Ala*], 0.54 [ddd, $J=14.4$, 4.8, 4.8 Hz, 1H, 3-H_b, (*3-Ncp*)*Ala*], 0.90 (t, $J=7.2$ Hz, 3H, 5-H, *Ile*), 0.98–1.05 [m, 1H, 3′-H_b, (*3-Ncp*)*Ala*], 1.03 [ddd, $J=7.2$, 7.2, 7.2 Hz, 1H, 3′-H_a, (*3-Ncp*)*Ala*], 1.07 (d, $J=7.2$ Hz, 3H, 1′-H, *Ile*), 1.32 [d, $J=7.2$ Hz, 3H, 4-H, (β*Me*)*Phe*], 1.35 [d, $J=7.2$ Hz, 3H, 4-H, (β*Me*)*Phe*], 1.41 (d, $J=7.8$ Hz, 3H, *a-Dab*), 1.53–1.59 (m, 1H, 4-H_b, *Ile*), 1.63–1.75 [m, 2H, 3-H, (*3-Ncp*)*Ala*], 1.69 [dd, $J=7.2$, 1.8 Hz, 3H, 3′-H, (*4-Pe*)*Pro*], 1.84–1.95 [m, 3H, 3′-H_b, (*3-Ncp*)*Ala*, 3-H, *Ile*, 3-H_a, (*4-Pe*)*Pro*], 1.95–2.01 [m, 1H, 3-H_a, (*4-Pe*)*Pro*], 2.27 [ddd, $J=12.0$, 6.0, 6.0 Hz, 1H, 4-H_b, (*4-Pe*)*Pro*], 2.85 [ddd, $J=6.6$, 4.8, 4.8 Hz, 1H, 2′-H, (*3-Ncp*)*Ala*], 3.02 [dq, $J=11.4$, 7.2 Hz, 1H, 3-H, (β*Me*)*Phe*], 3.22–3.32 [m, 2H, 4-H, 5-H_a, (*4-Pe*)*Pro*], 3.46–3.52 [m, 1H, 2-H, (*3-Ncp*)*Ala*], 3.70 [dq, $J=3.6$, 7.2 Hz, 1H, 3-H, (β*Me*)*Phe*], 3.92 [dd, $J=11.4$, 5.4 Hz, 2-H, (*4-Pe*)*Pro*], 3.95–3.99 [m, 1H, 5-H_b, (*4-Pe*)*Pro*], 4.03 [ddd, $J=7.2$, 3.6, 3.6 Hz, 1H, 2′-H, (*3-Ncp*)*Ala*], 4.35 (dd, $J=10.8$, 10.8 Hz, 1H, 2-H), 4.42–4.48 (m, 1H, 3-H, *a-Dab*), 4.45 (dd, $J=10.2$, 4.2 Hz, 1H, 2-H), 4.50 (dd, $J=9.0$, 3.0 Hz, 1H, 2-H), 4.66 (dd, $J=9.0$, 9.0 Hz, 1H, 2-H), 5.11–5.16 [m, 1H, 2-H, (*3-Ncp*)*Ala*], 5.26–5.31 [m, 1H, 1′-H, (*4-Pe*)*Pro*], 5.63 [dq, $J=10.8$, 6.6 Hz, 1H, 2′-H, (*4-Pe*)*Pro*], 6.15 (d, $J=4.2$ Hz, 1H, 4-H, *Chpca*), 6.43 (d, $J=7.8$ Hz, 1H, NH), 6.77–6.86 (br, 1H, NH), 6.85 (d, $J=4.2$ Hz, 1H, 3-H, *Chpca*), 7.02–7.06 (m, 2H, Ar-H), 7.12–7.19 (m, 6H, Ar-H, NH), 7.21–7.30 (m, 4H, Ar-H, NH), 7.44 (d, $J=10.8$ Hz, 1H, NH), 8.87 (d, $J=9.0$ Hz, 1H, NH), 10.70–11.00 (br, 1H, OH); the signal of 4-H_a, *Ile* was masked by absorption of 4-H, (β*Me*)*Phe* (1.35 ppm); ^{13}C NMR (150.8 MHz, $CDCl_3$): $\delta=10.4$ (+, C-5, *Ile*), 13.1 [+, C-3′, (*4-Pe*)*Pro*], 13.3 (+, C-4, *a-Dab*), 14.9 (+, C-1′, *Ile*), 17.0 [−, C-3′, (*3-Ncp*)*Ala*], 17.2 [−, C-3′, (*3-Ncp*)*Ala*], 17.6 [+, C-4, (β*Me*)*Phe*], 17.7 [+, C-4, (β*Me*)*Phe*], 20.0 [+, C-1′, (*3-Ncp*)*Ala*], 21.7 [+, C-1′, (*3-Ncp*)*Ala*], 25.1 (−, C-4, *Ile*), 32.8 [−, C-3, (*3-Ncp*)*Ala*], 35.2 [−, C-3, (*3-Ncp*)*Ala*], 35.9 [−, C-3, (*4-Pe*)*Pro*], 36.4 [+, C-4, (*4-Pe*)*Pro*], 38.0 (+, C-3, *Ile*), 39.2 [+, C-3, (β*Me*)*Phe*], 41.2 [+, C-3, (β*Me*)*Phe*], 45.3 (+, C-3, *a-Dab*), 51.0 [+, C-2, (*3-Ncp*)*Ala*], 51.8 [+, C-2, (*3-Ncp*)*Ala*], 53.1 [−, C-5, (*4-Pe*)*Pro*], 54.6 (+, C-2), 55.2 (+, C-2), 58.1 [+, C-2′, (*3-Ncp*)*Ala*], 59.3 [+, C-2′, (*3-Ncp*)*Ala*], 59.8 (+, C-2), 60.0 (+, C-2), 63.8 [+, C-2, (*4-Pe*)*Pro*], 103.6 (+, C-4, *Chpca*), 109.9 (+, C-3, *Chpca*), 119.9 (C_{quat}, C-2, *Chpca*), 121.7 (C_{quat}, C-5, *Chpca*), 126.9, 127.3, 127.4, 127.6 (+, Ar-C), 127.87 [+, C-1′, (*4-Pe*)*Pro*], 127.92 [+, C-2′, (*4-Pe*)*Pro*], 128.5, 128.7 (+, Ar-C), 141.3, 142.2 (C_{quat}, Ar-C), 159.3 (C_{quat}, C-1, *Chpca*), 168.3, 169.6, 170.0, 170.2, 171.60, 171.62, 171.9 (C_{quat}, C-1); IR (KBr): $\tilde{\nu}=3383$, 2968, 2933, 2879, 1747, 1651, 1626, 1548, 1452, 1372, 1321, 1182 cm^{-1}; UV (MeOH): neutral: $\lambda_{max}(\varepsilon)=277$ (1.6×10^4) nm; basic: 281 (1.5×10^4), 205 (7.0×10^4) nm; acidic: 272 (1.4×10^4) nm; CD (MeOH): $\lambda_{max}[\Theta]=280.2$ (2.01×10^4); 276.5 (2.05×10^4), 225.6 (-4.55×10^4), 221.5 (-5.06×10^4) nm ($c=1.45\times10^{-5}$ M); MS (ESI): pos.: *m/z* (%): 1151 (100) [*M*+Na^+]; neg.: *m/z* (%): 1127 (100) [*M*−H^-]; HRMS (ESI): *m/z*: calcd for [$C_{55}H_{71}N_{11}O_{13}Cl^+$]: 1128.4916; found 1128.4921.

[*a*-Dab^1,*a*-Ile^5]-Hormaomycin (*epi*-2a): A solution (50 mL) of the CHA salt of Teoc-(2*S*,1′*R*,2′*R*)-(3-Ncp)AlaOH (27.3 mg, 65.39 μmol) in Et_2O (50 mL) was washed with 1 M H_2SO_4 (3×5 mL), 1 M $KHSO_4$ (2×5 mL), water (3×5 mL), brine (2×5 mL), dried, filtered and concentrated under reduced pressure. The resulting *N*-protected amino acid was dried at 0.02 Torr for 2 h and then coupled with the depsipeptide, obtained after deprotection of *epi*-**19a** (20.0 mg, 20.47 μmol) by treatment with 10% anisole in TFA (1.1 mL) according to GP 6 for 2 h, applying HATU (23.4 mg, 61.54 μmol), HOAt (8.3 mg, 61.42 μmol), DIEA (2.64 mg, 20.39 μmol) and TMP (22.36 mg, 183.6 μmol) in CH_2Cl_2 (3 mL) according to GP 4 for 15 h. The mixture was then diluted with Et_2O (40 mL), and the crude product obtained after the usual aqueous work-up (GP 2) was purified by two crystallizations from Et_2O/hexane to give the respective Teoc-(*S*)-(3-Ncp)Ala-*epi*-cyclohexapeptide (17.0 mg, 74%; $R_f=0.19$, acetone/hexane 1:2.5) as a colorless glass which was used for the next step without any characterization. This substance (17.0 mg, 14.50 μmol) was deprotected by treatment with TFA (2.0 mL) for 1 h. The mixture was concentrated under reduced pressure at 20 °C, and then taken up with toluene (3×15 mL) which was distilled off to remove the last traces of TFA. The resulting deprotected branched peptide was coupled with Chpca(MOM)-OH **20** (5.5 mg, 26.74 μmol) applying HATU (10.15 mg, 26.69 μmol), DIEA (1.95 mg, 15.09 μmol) and TMP (12.37 mg, 102.08 μmol) in CH_2Cl_2 (3 mL) according to GP 4 for 5 h. The mixture was then diluted with Et_2O (40 mL), and the crude product obtained after the usual aqueous work-up (GP 2) was recrystallized twice from CH_2Cl_2/hexane to give the *O*-MOM protected [*a*-Dab^1,*a*-Ile^5]-hormaomy-

cin (14.2 mg, 80%; R_f=0.11, acetone/hexane 1:3) as a colorless solid which was used for the next step without any characterization. MOM-*epi*-**2a** (14.2 mg, 12.11 μmol) was deprotected applying $MgBr_2{\cdot}Et_2O$ (110 mg, 425.17 μmol) and EtSH (0.018 mL, 243.07 μmol) in CH_2Cl_2 (10 mL) according to GP 7 for 3 h. The mixture was taken up with Et_2O (50 mL), and the crude product obtained after the usual aqueous work-up (GP 7) was recrystallized from Et_2O/pentane and then from CH_2Cl_2/pentane to give the crude product (13.1 mg), which was finally purified by preparative HPLC to give *epi*-**2a** (9.0 mg, 39% over five steps from *epi*-**19a**) as a colorless solid, which was insoluble in $CHCl_3$. R_f=0.14, acetone/hexane 1:2.5; preparative HPLC: column B, 62% MeCN in H_2O (0.07% TFA), flow rate=2.5 mL min^{-1}; analytical HPLC: the same column, the same conditions, t_R=17.72 min, purity > 99%; ^{1}H NMR (600 MHz, CD_3OD): δ=0.69 (t, J=7.2 Hz, 3H, 5-H, *a-Ile*), 0.72 (d, J=7.2 Hz, 3H, 1′-H, *a-Ile*), 0.82–0.92 (m, 1H, 4-H$_a$, *a-Ile*), 0.95 (ddd, J=7.2, 7.2, 7.2 Hz, 1H, 4-H$_b$, *Ile*), 1.00 [ddd, J=6.0, 6.0, 6.0 Hz, 1H, 3′-H$_a$, (*3-Ncp*)*Ala*], 1.07 [ddd, J=6.6, 6.6, 6.6 Hz, 1H, 3′-H$_a$, (*3-Ncp*)*Ala*], 1.14 [d, J=6.6 Hz, 3H, 4-H, (β*Me*)*Phe*], 1.25 [d, J=7.2 Hz, 3H, 4-H, (β*Me*)*Phe*], 1.31 (d, J=7.2 Hz, 3H, *a-Dab*), 1.34–1.41 [m, 1H, 3-H$_a$, (*3-Ncp*)*Ala*], 1.44–1.52 [m, 1H, 3-H$_a$, (*3-Ncp*)*Ala*], 1.54–1.60 [m, 1H, 3′-H$_b$, (*3-Ncp*)*Ala*], 1.65 [dd, J=7.2, 1.8 Hz, 3H, 3′-H, (*4-Pe*)*Pro*], 1.82 [ddd, J=7.8, 7.8, 7.8 Hz, 1H, 3-H$_a$, (*4-Pe*)*Pro*], 1.93–2.01 [m, 2H, 3-H$_b$, 1′-H, (*3-Ncp*)*Ala*], 2.03–2.15 [m, 2H, 3-H$_b$, (*3-Ncp*)*Ala*, 3-H$_b$, (*4-Pe*)*Pro*], 2.98 [dd, J=10.8, 10.8 Hz, 1H, 5-H$_a$, (*4-Pe*)*Pro*], 3.07 [m, 1H, 4-H, (*4-Pe*)*Pro*], 3.13–3.24 [m, 2H, 2×3-H, (β*Me*)*Phe*], 3.69 [dd, J=10.8, 7.2 Hz, 1H, 5-H$_b$, (*4-Pe*)*Pro*], 4.08 [ddd, J=6.6, 3.0, 3.0 Hz, 1H, 2′-H, (*3-Ncp*)*Ala*], 4.10–4.14 (m, 1H, 2-H, *a-Ile*), 4.19–4.29 [m, 3H, 3-H, *a-Dab*, 2-H, 2′-H, (*3-Ncp*)*Ala*], 4.40 [d, J=10.8 Hz, 2-H, (β*Me*)*Phe*], 4.49 (d, J=3.6 Hz, 1H, 2-H, *a-Dab*), 4.51 [dd, J=7.8, 7.8 Hz, 1H, 2-H, (*4-Pe*)*Pro*], 4.77 [d, J=11.4 Hz, 1H, 2-H, (β*Me*)*Phe*], 4.79–4.82 [m, 1H, 2-H, (*3-Ncp*)*Ala*], 5.38–5.44 [m, 1H, 1′-H, (*4-Pe*)*Pro*], 5.59 [dq, J=10.2, 7.2 Hz, 1H, 2′-H, (*4-Pe*)*Pro*], 6.00 (d, J=4.5 Hz, 1H, 4-H, *Chpca*), 6.73 (d, J=4.5 Hz, 1H, 3-H, *Chpca*), 7.01–7.15 (m, 1H, Ar-H), 7.17–7.25 (m, 3H, Ar-H), 7.25–7.31 (m, 6H, Ar-H), 7.41–7.49 (br, 1H, NH), 7.80–7.84 (br, 1H, NH); the signal of 1′-H, (*3-Ncp*)*Ala* was masked by absorption of 4-H, *a-Dab* and the signals of 3-H, *a-Ile* and 3′-H$_b$, (*3-Ncp*)*Ala* were masked by absorption of 3′-H, (*4-Pe*)*Pro*; ^{13}C NMR (150.8 MHz, CD_3OD): δ=12.2 (+, C-5, *a-Ile*), 13.3 [+, C-3′, (*4-Pe*)*Pro*], 14.6 (+, C-1′, *a-Ile*), 17.9 [−, C-3′, (*3-Ncp*)*Ala*], 18.0 [+, C-4, (β*Me*)*Phe*], 18.9 [−, C-3′, (*3-Ncp*)*Ala*], 19.1 (+, C-4, *a-Dab*), 19.4 [+, C-4, (β*Me*)*Phe*], 23.6 [+, C-1′, (*3-Ncp*)*Ala*], 23.8 [+, C-1′, (*3-Ncp*)*Ala*], 27.3 (−, C-4, *a-Ile*), 34.06 [−, C-3, (*3-Ncp*)*Ala*], 34.15 [−, C-3, (*3-Ncp*)*Ala*], 34.18 [−, C-3, (*4-Pe*)*Pro*], 36.5 (+, C-3, *a-Ile*), 37.7 [+, C-4, (*4-Pe*)*Pro*], 41.6 [+, C-3, (β*Me*)*Phe*], 43.4 [+, C-3, (β*Me*)*Phe*], 48.9 (+, C-3, *a-Dab*), 51.0 [+, C-2, (*3-Ncp*)*Ala*], 53.2 [−, C-5, (*4-Pe*)*Pro*], 53.3 [+, C-2′, (*3-Ncp*)*Ala*], 53.9 [+, C-2, (*3-Ncp*)*Ala*], 55.9 (+, C-2, *a-Ile*), 58.4 (+, C-2, *a-Dab*), 59.5 [+, C-2, (β*Me*)*Phe*], 60.2 [+, C-2, (*3-Ncp*)*Ala*], 60.3 [+, C-2′, (*3-Ncp*)*Ala*], 61.3 [+, C-2, (*4-Pe*)*Pro*], 62.0 [+, C-2, (β*Me*)*Phe*], 104.0 (+, C-4, *Chpca*), 111.1 (+, C-3, *Chpca*), 119.2 (C_{quat}, C-2, *Chpca*), 122.1 (C_{quat}, C-5, *Chpca*), 127.5 [+, C-2′, (*4-Pe*)*Pro*], 127.8, 128.2, 128.95, 128.99, 129.59, 129.67 (+, Ar-C), 130.8 [+, C-1′, (*4-Pe*)*Pro*], 143.6, 144.5 (C_{quat}, Ar-C), 161.7 (C_{quat}, C-1, *Chpca*), 171.3, 172.0, 172.2, 172.7, 172.87, 172.90, 174.3 (C_{quat}, C-1); IR (KBr): $\tilde{\nu}$=3445, 2926, 2850, 1653, 1558, 1543, 1458, 1383, 1321, 1020 cm^{-1}; UV (MeOH): neutral: $\lambda_{max}(\varepsilon)$=279 ($8.3\times10^3$) nm; basic: 283 ($8.0\times10^3$), 209 ($2.3\times10^4$) nm; acidic: 271 ($8.7\times10^3$) nm; CD (MeOH): $\lambda_{max}[\Theta]$=279.6 (1.15×10^4); 275.7 (1.08×10^4), 225.3 (-3.85×10^4) nm ($c=1.26\times10^{-5}$ M); MS (ESI): pos.: *m/z* (%): 1151 (100) [M+Na$^+$], 1129 (52) [M+H$^+$]; neg.: *m/z* (%): 1127 (100) [M−H$^-$].

[*a*-N$_\beta$Me-Dab^1]-Hormaomycin (2b): A solution of the CHA salt of Teoc-(2*S*,1′*R*,2′*R*)-(3-Ncp)AlaOH (40.3 mg, 96.5 μmol) in Et_2O (50 mL) was washed with 1 M H_2SO_4 (3×5 mL), 1 M $KHSO_4$ (2×5 mL), water (3×5 mL), brine (2×5 mL), dried, filtered and concentrated under reduced pressure. The resulting *N*-protected amino acid was dried at 0.02 Torr for 2 h and then coupled with the peptolide, obtained after deprotection of **19b** (29.0 mg, 29.3 μmol) by treatment with 10% anisole in TFA (1.5 mL) according to GP 6 for 2 h, applying HATU (33.3 mg, 87.8 μmol), HOAt (13.0 mg, 96.5 μmol), DIEA (3.78 mg, 29.3 μmol) and TMP (31.9 mg, 263.3 μmol) in CH_2Cl_2 (3 mL) according to GP 4 for 15 h. The mixture was then diluted with Et_2O (40 mL), and the crude product obtained after the usual aqueous work-up (GP 2) was purified by crystallization first from CH_2Cl_2/pentane and then from Et_2O/pentane to give the respective Teoc-(*S*)-(3-Ncp)Ala-cyclohexapeptide (32.5 mg, 97%; R_f=0.22, acetone/hexane 4:7) as a colorless solid, which was used for the next step without any characterization. This substance (32.5 mg, 28.4 μmol) was deprotected by treatment with TFA (2.0 mL) for 1 h. The mixture was concentrated under reduced pressure at 20 °C and then taken up with toluene (3×15 mL) which was distilled off to remove the last traces of TFA. The resulting deprotected branched peptide was coupled with Chpca(MOM)-OH **20** (14.6 mg, 71.1 μmol) applying HATU (25.9 mg, 68.2 μmol), DIEA (3.67 mg, 28.4 μmol) and TMP (26.0 mg, 213.0 μmol) in CH_2Cl_2 (3 mL) according to GP 4 for 5 h. The mixture was then diluted with Et_2O (40 mL), and the crude product obtained after the usual aqueous work-up (GP 2) was purified by chromatography (R_f=0.39, acetone/hexane 1:1.5) to give the *O*-MOM protected [*a*-N$_\beta$Me-Dab^1]-hormaomycin (25.0 mg, 74%) as a colorless solid, which was used for the next step without any characterization. MOM-**2b** (25.0 mg, 21.1 μmol) was deprotected by treatment with $MgBr_2{\cdot}Et_2O$ (150 mg, 579.7 μmol) and EtSH (0.015 mL, 202.6 μmol) in CH_2Cl_2 (10 mL) according to GP 7 for 3.5 h. The mixture was diluted Et_2O (50 mL), and the crude product obtained after the usual aqueous work-up (GP 7) was recrystallized from CH_2Cl_2/pentane to give a crude product (22.0 mg), which was finally purified by preparative HPLC to give **2b** (16.0 mg, 48% over five steps) as a colorless solid. Preparative HPLC: column B, 69% MeCN in H_2O (0.1% TFA), flow rate=2.5 mL min^{-1}; analytical HPLC: 70% MeCN in H_2O (0.1% TFA), flow rate=0.5 mL min^{-1}, t_R=10.00 min, purity > 99%; R_f=0.24, acetone/hexane 1:1.5; $[\alpha]_D^{20}$=75.0 (c=0.15, MeOH); ^{1}H NMR (600 MHz, $CDCl_3$): δ=−0.01–0.16 [m, 2H, 3-H$_a$, 3′-H$_a$, (*3-Ncp*)*Ala*], 0.64–0.76 [m, 1H, 1′-H, (*3-Ncp*)*Ala*], 0.81 (t, J=7.2 Hz, 3H, 5-H, *Ile*), 1.03 (d, J=6.6 Hz, 3H, 1′-H, *Ile*), 1.15–1.25 (m, 1H, 4-H$_a$, *Ile*), 1.26 [d, J=6.6 Hz, 3H, 4-H, (β*Me*)*Phe*], 1.37 [d, J=7.2 Hz, 3H, 4-H, (β*Me*)*Phe*], 1.45–1.53 (m, 1H, 4-H$_b$, *Ile*), 1.55 (d, J=7.2 Hz, 3H, *a-N*$_\beta$*Me-Dab*), 1.66 [dd, J=6.6, 1.2 Hz, 3H, 3′-H, (*4-Pe*)*Pro*], 1.70–1.79 [m, 3H, 3-H, (*3-Ncp*)*Ala*, 3-H$_a$, (*4-Pe*)*Pro*], 1.83–1.88 [m, 1H, 3′-H$_b$, (*3-Ncp*)*Ala*], 1.94–2.02 [m, 1H, 3-H, *Ile*], 2.03–2.10 [m, 1H, 1′-H, (*3-Ncp*)*Ala*], 2.17–2.23 [m, 1H, 4-H$_b$, (*4-Pe*)*Pro*], 2.85 [dq, J=9.6, 6.6 Hz, 1H, 3-H, (β*Me*)*Phe*], 3.10 (s, 3H, NMe, *a-N*$_\beta$*Me-Dab*), 3.20–3.34 [m, 3H, 4-H, 5-H$_a$, (*4-Pe*)*Pro*, 2′-H, (*3-Ncp*)*Ala*], 3.54–3.60 [m, 1H, 2-H, (*3-Ncp*)*Ala*], 3.70 [dq, J=5.2, 7.2 Hz, 1H, 3-H, (β*Me*)*Phe*], 4.02 [dd, J=7.2, 7.2 Hz, 1H, 5-H$_b$, (*4-Pe*)*Pro*], 4.19–4.24 [m, 1H, 2′-H, (*3-Ncp*)*Ala*], 4.50 [dd, J=9.6 Hz, 1H, 2-H, (β*Me*)*Phe*], 4.52 [dd, J=12.0, 5.2 Hz, 1H, 2-H, (β*Me*)*Phe*], 4.59–4.64 [m, 4H, 2-H, *Ile*, 2-H, 3-H, *a-N*$_\beta$*Me-Dab*, 2-H, (*4-Pe*)*Pro*], 4.98–5.02 [m, 1H, 2-H, (*3-Ncp*)*Ala*], 5.24–5.29 [m, 1H, 1′-H, (*4-Pe*)*Pro*], 5.60 [dq, J=11.2, 6.6 Hz, 1H, 2′-H, (*4-Pe*)*Pro*], 5.98–6.01 (m, 1H, 4-H, *Chpca*), 6.60–6.67 (m, 1H, 3-H, *Chpca*), 6.64–6.71 (br, 1H, NH), 7.02–7.08 (m, 2H, Ar-H), 7.10–7.19 (m, 4H, Ar-H, NH), 7.16–7.20 (m, 2H, Ar-H), 7.22–7.28 (m, 4H, Ar-H, NH), 7.34–7.40 (br, 1H, NH), 7.40–7.47 (br, 1H, NH), 7.98–8.10 (br, 1H, NH), 8.52–8.62 (br, 1H, NH), 12.0–13.2 (br, 1H, OH); the signals of 3-H$_b$, (*3-Ncp*)*Ala* and 3′-H$_b$, (*3-Ncp*)*Ala* was masked by absorption of 1′-H, *Ile* and the signal of 3′-H$_b$, (*3-Ncp*)*Ala* by absorption of 4-H, (β*Me*)*Phe* (1.26 ppm); ^{13}C NMR (150.8 MHz, $CDCl_3$): δ=10.4 (+, C-5, *Ile*), 13.26 [+, C-4, (β*Me*)*Phe*], 13.31 [+, C-3′, (*4-Pe*)*Pro*], 15.4 (+, C-1′, *Ile*), 16.6 (+, C-4, *a-N*$_\beta$*Me-Dab*), 17.0 [−, C-3′, (*3-Ncp*)*Ala*], 17.2 [−, C-3′, (*3-Ncp*)*Ala*], 18.0 [+, C-4, (β*Me*)*Phe*], 20.7 [+, C-1′, (*3-Ncp*)*Ala*], 21.9 [+, C-1′, (*3-Ncp*)*Ala*], 24.7 (−, C-4, *Ile*), 32.4 (+, NMe, *a-N*$_\beta$*Me-Dab*), 32.6 [−, C-3, (*3-Ncp*)*Ala*], 33.5 [−, C-3, (*3-Ncp*)*Ala*], 34.8 [−, C-3, (*4-Pe*)*Pro*], 36.6 (+, C-3, *Ile*), 36.8 [+, C-4, (*4-Pe*)*Pro*], 39.1 [+, C-3, (β*Me*)*Phe*], 43.7 [+, C-3, (β*Me*)*Phe*], 50.6 [+, C-2, (*3-Ncp*)*Ala*], 52.3 (+, C-3, *a-N*$_\beta$*Me-Dab*), 52.60 [+, C-2, (*3-Ncp*)*Ala*], 52.65 [−, C-5, (*4-Pe*)*Pro*], 54.9 (+, C-2, *Ile*), 58.6 [+, C-2′, (*3-Ncp*)*Ala*], 58.8 (+, C-2, *a-N*$_\beta$*Me-Dab*), 58.9 [+, C-2, (β*Me*)*Phe*], 59.4 [+, C-2′, (*3-Ncp*)*Ala*], 59.5 [+, C-2, (β*Me*)*Phe*], 59.6 [+, C-2, (*4-Pe*)*Pro*], 103.1 (+, C-4, *Chpca*), 108.5 (+, C-3, *Chpca*), 117.7 (C_{quat}, C-2, *Chpca*), 119.0 (C_{quat}, C-5, *Chpca*), 126.8, 127.0, 127.3, 127.6 (+, Ar-C), 127.8 [+, C-1′, (*4-Pe*)*Pro*], 128.0 [+, C-2′, (*4-Pe*)*Pro*], 128.44 (×2) (+, Ar-C), 141.9, 142.3 (C_{quat}, Ar-C), 160.1 (C_{quat}, C-1, *Chpca*), 169.8, 170.0, 170.2, 170.7, 170.8, 171.2, 174.2 (C_{quat}, C-1); IR (KBr): $\tilde{\nu}$=3383, 2968, 2935, 2877, 1634, 1543, 1440, 1368, 1311, 1263, 1212, 1129 cm^{-1}; UV (MeOH): neutral: $\lambda_{max}(\varepsilon)$=277 ($1.5\times10^4$) nm; basic: 281 ($1.3\times10^4$), 205

(7.0×10^4) nm; acidic: 273 (1.6×10^4) nm; CD (MeOH): $\lambda_{max}[\Theta]=278.8$ (3.4×10^4); 229.0 (-2.54×10^4) nm ($c=2.1\times10^{-5}$ M); MS (ESI): pos.: *m*/*z* (%): 1165 (100) [*M*+Na$^+$]; neg.: *m*/*z* (%): 1141 (100) [*M*−H$^-$]; HRMS (ESI): *m*/*z*: calcd for [$C_{56}H_{73}N_{11}O_{13}Cl^+$]: 1142.5072; found 1142.5072.

[Dap^1]-Hormaomycin (2c): A solution of the CHA salt of Teoc-(2*S*,1′*R*,2′*R*)-(3-Ncp)AlaOH (40.6 mg, 97.3 μmol) in Et_2O (50 mL) was washed with 1 M H_2SO_4 (3×5 mL), 1 M $KHSO_4$ (2×5 mL), water (3×5 mL), brine (2×5 mL), dried, filtered and concentrated under reduced pressure. The resulting *N*-protected amino acid was dried at 0.02 Torr for 2 h and then coupled with the peptolide, obtained after deprotection of **19c** (28.4 mg, 29.5 μmol) by treatment with 10% anisole in TFA (1.5 mL) according to GP 6 for 2 h, applying HATU (33.6 mg, 88.5 μmol), HOAt (13.2 mg, 97.3 μmol), DIEA (3.81 mg, 29.5 μmol) and TMP (32.2 mg, 265.4 μmol) in CH_2Cl_2 (3 mL) according to GP 4 for 15 h. The mixture was then diluted with Et_2O (40 mL), and the crude product obtained after the usual aqueous work-up (GP 2) was purified by crystallization first from CH_2Cl_2/pentane and then from Et_2O/pentane to give the respective Teoc-(*S*)-(3-Ncp)Ala-cyclohexapeptide (30.2 mg, 92%; $R_f=0.25$, acetone/hexane 4:7) as a colorless solid, which was used for the next step without any characterization. This substance (30.2 mg, 27.1 μmol) was deprotected by treatment with TFA (2.0 mL) for 1 h. The mixture was concentrated under reduced pressure at 20 °C and then taken up with toluene (3×15 mL), which was distilled off to remove the last traces of TFA. The resultant deprotected branched peptide was coupled with Chpca-(MOM)-OH **20** (13.9 mg, 67.7 μmol) applying HATU (23.7 mg, 62.3 μmol), DIEA (3.50 mg, 27.1 μmol) and TMP (25.0 mg, 203.1 μmol) in CH_2Cl_2 (3 mL) according to GP 4 for 5 h. The mixture was then diluted with Et_2O (40 mL), and the crude product obtained after the usual aqueous work-up (GP 2) was purified by chromatography (acetone/hexane 1:1.5) to give the *O*-MOM protected [Dap^1]-hormaomycin (22.0 mg, 70%; $R_f=0.10$, acetone/hexane 4:7) as a colorless solid, which was used for the next step without any characterization. MOM-**2c** (22.0 mg, 21.1 μmol) was deprotected by treatment with $MgBr_2\cdot Et_2O$ (150 mg, 579.7 μmol) and EtSH (0.015 mL, 202.6 μmol) in CH_2Cl_2 (10 mL) according to GP 7 for 3.5 h. The mixture was diluted Et_2O (50 mL), and the crude product obtained after the usual aqueous work-up (GP 7) was recrystallized from CH_2Cl_2/pentane to give a crude product (21.5 mg), which was finally purified by preparative HPLC to give **2c** (14.2 mg, 43% over five steps) as a colorless solid. Preparative HPLC: column B, 70% MeCN in H_2O (0.1% TFA), flow rate = 2.5 mL min^{-1}; analytical HPLC: 70% MeCN in H_2O (0.1% TFA), flow rate = 0.5 mL min^{-1}, $t_R=9.27$ min, purity > 99%; $R_f=0.10$ (acetone/hexane 4:7); $[\alpha]_D^{20}=61.0$ ($c=0.10$, MeOH); ^{1}H NMR (600 MHz, $CDCl_3$): $\delta=-0.60$ [ddd, $J=6.6$, 6.6, 6.6 Hz, 1H, 3′-H$_a$, (*3-Ncp*)*Ala*], −0.20–0.02 [m, 1H, 3-H$_a$, (*3-Ncp*)*Ala*], 0.25–0.31 [m, 1H, 1′-H, (*3-Ncp*)*Ala*], 0.52 [ddd, $J=13.8$, 4.8, 4.8 Hz, 1H, 3-H$_b$, (*3-Ncp*)*Ala*], 0.89 (t, $J=7.2$ Hz, 3H, 5-H, *Ile*), 0.98–1.05 [m, 2H, 3′-H$_a$, 3′-H$_b$, (*3-Ncp*)*Ala*], 1.07 (d, $J=7.2$ Hz, 3H, 1′-H, *Ile*), 1.30 [d, $J=7.2$ Hz, 3H, 4-H, (β*Me*)*Phe*], 1.40 [d, $J=7.2$ Hz, 3H, 4-H, (β*Me*)*Phe*], 1.54–1.60 (m, 1H, 4-H$_b$, *Ile*), 1.67 [dd, $J=6.6$ Hz, 3H, 3′-H, (*4-Pe*)*Pro*], 1.67–1.75 [m, 2H, 3-H, (*3-Ncp*)*Ala*], 1.84–1.93 [m, 3H, 3′-H$_b$, (*3-Ncp*)*Ala*, 3-H, *Ile*, 3-H$_a$, (*4-Pe*)*Pro*], 1.95–2.01 [m, 1H, 3-H$_a$, (*4-Pe*)*Pro*], 2.23 [ddd, $J=12.0$, 6.0, 6.0 Hz, 1H, 4-H$_b$, (*4-Pe*)*Pro*], 2.87 [ddd, $J=6.6$, 3.0, 3.0 Hz, 1H, 2′-H, (*3-Ncp*)*Ala*], 3.04 [dq, $J=10.5$, 7.2 Hz, 1H, 3-H, (β*Me*)*Phe*], 3.18–3.30 [m, 2H, 4-H, 5-H$_a$, (*4-Pe*)*Pro*], 3.33 (d, $J=13.8$ Hz, 1H, 3-H$_a$, *Dap*), 3.49 [ddd, $J=7.2$, 3.6 Hz, 1H, 2-H, (*3-Ncp*)*Ala*], 3.68 [dq, $J=4.8$, 7.2 Hz, 1H, 3-H, (β*Me*)*Phe*], 3.93 [dd, $J=12.0$, 5.4 Hz, 2-H, (*4-Pe*)*Pro*], 3.94–3.98 [m, 1H, 5-H$_b$, (*4-Pe*)*Pro*], 4.04 [ddd, $J=7.2$, 3.6, 3.6 Hz, 1H, 2′-H, (*3-Ncp*)*Ala*], 4.16 (dddd, $J=13.8$, 10.8, 3.0, 3.0 Hz, 1H, 3-H$_b$, *Dap*), 4.33 [dd, $J=10.5$, 10.5 Hz, 1H, 2-H, (β*Me*)*Phe*], 4.47 [dd, $J=9.6$, 4.8 Hz, 1H, 2-H, (β*Me*)*Phe*], 4.50 (dd, $J=9.0$, 3.0 Hz, 1H, 2-H), 4.60–4.68 (m, 2H, 2-H, *Ile*, 2-H, *Dap*), 5.14–5.20 [m, 1H, 2-H, (*3-Ncp*)*Ala*], 5.24–5.30 [m, 1H, 1′-H, (*4-Pe*)*Pro*], 5.61 [dq, $J=10.8$, 6.6 Hz, 1H, 2′-H, (*4-Pe*)*Pro*], 6.15 (d, $J=4.8$ Hz, 1H, 4-H, *Chpca*), 6.46 (d, $J=6.6$ Hz, 1H, NH), 6.78–6.83 (br, 1H, NH), 6.83 (d, $J=4.8$ Hz, 1H, 3-H, *Chpca*), 7.02–7.06 (m, 2H, Ar-H), 7.10–7.19 (m, 6H, Ar-H, NH), 7.20–7.24 (m, 5H, Ar-H, NH), 7.32 (d, $J=9.0$ Hz, 1H, NH), 8.17 (d, $J=7.8$ Hz, 1H, NH), 8.75 (d, $J=8.4$ Hz, 1H, NH), 10.75–11.15 (br, 1H, OH); The signal of 4-H$_a$, *Ile* was masked by absorption of C-4, (β*Me*)*Phe* (1.30 ppm); ^{13}C NMR (150.8 MHz, $CDCl_3$): $\delta=10.3$ (+, C-5, *Ile*), 13.2 [+, C-4, (β*Me*)*Phe*], 13.3 [+, C-3′, (*4-Pe*)*Pro*], 14.8 (+, C-1′, *Ile*), 16.9 [−, C-3′, (*3-Ncp*)*Ala*], 17.1 [−, C-3′, (*3-Ncp*)*Ala*], 17.5 [+, C-4, (β*Me*)*Phe*], 20.0 [+, C-1′, (*3-Ncp*)*Ala*], 21.6 [+, C-1′, (*3-Ncp*)*Ala*], 25.1 (−, C-4, *Ile*), 32.9 [−, C-3, (*3-Ncp*)*Ala*], 35.0 [−, C-3, (*3-Ncp*)*Ala*], 35.7 [−, C-3, (*4-Pe*)*Pro*], 36.3 [+, C-4, (*4-Pe*)*Pro*], 37.8 (+, C-3, *Ile*), 38.0 (−, C-3, *Dap*), 39.1 [+, C-3, (β*Me*)*Phe*], 41.6 [+, C-3, (β*Me*)*Phe*], 50.9 [+, C-2, (*3-Ncp*)*Ala*], 51.8 (+, C-2, *Dap*), 52.0 [+, C-2, (*3-Ncp*)*Ala*], 53.0 [−, C-5, (*4-Pe*)*Pro*], 54.5 (+, C-2, *Ile*), 58.0 [+, C-2′, (*3-Ncp*)*Ala*], 59.2 [+, C-2′, (*3-Ncp*)*Ala*], 60.0 [+, C-2, (β*Me*)*Phe*], 60.3 [+, C-2, (β*Me*)*Phe*], 63.5 [+, C-2, (*4-Pe*)*Pro*], 103.6 (+, C-4, *Chpca*), 109.8 (+, C-3, *Chpca*), 119.9 (C_{quat}, C-2, *Chpca*), 121.6 (C_{quat}, C-5, *Chpca*), 126.9, 127.3, 127.4, 127.6 (+, Ar-C), 127.8 [+, C-1′, (*4-Pe*)*Pro*], 127.9 [+, C-2′, (*4-Pe*)*Pro*], 128.5, 128.6 (+, Ar-C), 141.3, 142.1 (C_{quat}, Ar-C), 159.2 (C_{quat}, C-1, *Chpca*), 168.4, 169.5, 170.3, 170.8, 171.7, 172.4, 172.5 (C_{quat}, C-1); IR (KBr): $\tilde{\nu}=3347$, 2968, 2933, 2877, 1625, 1544, 1428, 1368, 1260, 1210 cm^{-1}; UV (MeOH): neutral: $\lambda_{max}(\varepsilon)=277$ (1.6×10^4), 209 (5.6×10^4) nm; basic: 280 (1.7×10^4), 211 (5.6×10^4) nm; acidic: 273 (1.6×10^4), 208 (5.6×10^4) nm; CD (MeOH): $\lambda_{max}[\Theta]=276.0$ (3.31×10^4); 222.6 (-3.47×10^4), 210.8 (-5.67×10^3) nm ($c=2.9\times10^{-5}$ M); MS (ESI): pos.: *m*/*z* (%): 1137 (100) [*M*+Na$^+$], 1115 (32) [*M*+H$^+$]; neg.: *m*/*z* (%): 1113 (72) [*M*−H$^-$]; HRMS (ESI): *m*/*z*: calcd for [$C_{54}H_{69}N_{11}O_{13}Cl^+$]: 1114.4759; found 1114.4760.

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