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Syntheses of hapalosin analogs by solid-phase assembly of acyclic precursors

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Abstract—The paper details the synthesis of hapalosin analogs **4** (cyclic depsipeptides) using solid-phase chemistry. Key building blocks were the Fmoc-protected γ-amino-β-hydroxy acid **11** and the THP-protected *syn*-β-hydroxy acids **18**. The amino acid **11** was fashioned from the amine **6** which was obtained by an ADH-route. The protected amino acids **18** were prepared by Evans aldol reactions. Esterification of **18** with the Wang resin started the solid-phase assembly of the depsipeptides **25** containing all the building blocks. A final solution-phase deprotection of the amino group followed by macrolactamization completed the synthesis of the analogs **4**. In one instance (compound **4aaa**) the conformation was studied using ROESY NMR spectroscopy and MD simulation. This revealed an almost complete (93:7) preference for the *s-cis*-rotamer.

1. Introduction

The importance of natural products for biochemistry and medicine is undisputed. Quite often natural products serve as biochemical tools or they lead to the discovery of a hitherto unknown biochemical pathway or molecular target. Nevertheless, in the context of the human genome project it was speculated that there might not be enough natural products to probe the functions of all genes via selective interaction of natural products with the corresponding proteins.[1] On the other hand natural products offer structurally interesting platforms, that might be used to produce natural product-like molecules. This way the chances of discovering novel modes of biological activity might be higher. With a view towards applying parallel or combinatorial synthesis strategies, natural products that are characterized by a modular built are obvious starting points.[2] Some representative examples include the indolactam library of Waldmann et al.,[3] the prostaglandin library of Janda,[4] the muscone library of Nicolaou,[5] or the carpanone library of Shair.[6] In this regard we have targeted the class of cyclic depsipeptides.[7] In these compounds one or more amide bonds are replaced with ester bonds. Very often depsipeptides contain unusual hydroxy acids or amino acids that pose a certain challenge from a synthetic point of view. Among the depsipeptides one might point out didemnin,[8] sanglifehrin A,[9] the AM-toxins I–III,[7] the cryptophycins (**1**),[10] jasplakinolide (**2**),[11] and hapalosin (**3**) (Fig. 1).[12]

In making these compounds even more peptide-like, some of the ester bonds could be replaced by amide bonds. Guided by the above-mentioned reasoning we became interested in the depsipeptide hapalosin (**3**). This natural compound is able to reverse multidrug resistance (MDR) in tumor cells. The phenomenon of MDR is caused by over-expression of the MDR1 gene that encodes for a 170 kDa P-glycoprotein. By virtue of its ability to block this transmembrane protein, hapalosin is an interesting lead compound for the development of drugs that can cope with resistant tumor cells. In fact, several syntheses of the natural product as well as some analogs have been reported.[13] Our own work in this area has resulted in two syntheses for the γ-amino-β-hydroxy acid **B**, whereby the first one is based on an Evans aldol/Curtius combination[14] and in the second route a Sharpless asymmetric dihydroxylation of an allylic chloride came to use.[15] In addition, we had reported the synthesis of hapalosin itself and some ring expanded analogs.[16] Due to its molecular structure hapalosin appears as a promising macrocycle for modifications in a parallel fashion. Taking into consideration our experience in the hapalosin area we decided to follow a strategy as shown in Fig. 2.

Thus, we planned to prepare some β-hydroxy acids **A** using an Evans aldol reaction. Also, we planned to replace the α-hydroxy acids with a range of α-amino acids **C**. While the syntheses of the γ-amino-β-hydroxy acid **B** would allow

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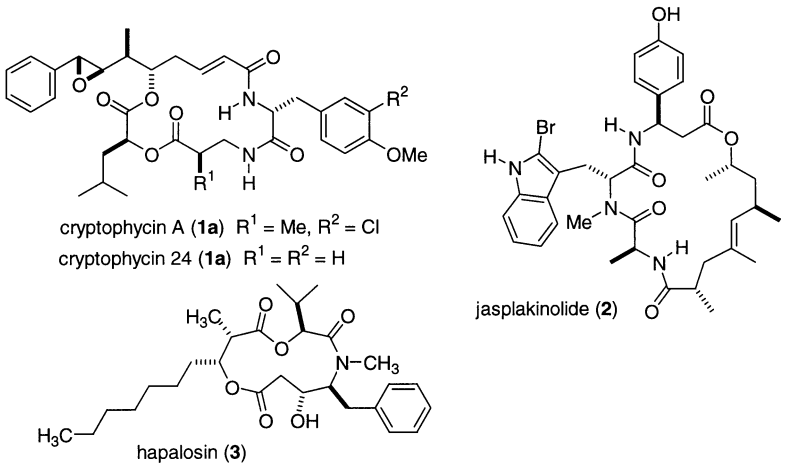


Figure 1. Structure of some representative cyclic depsipeptides.

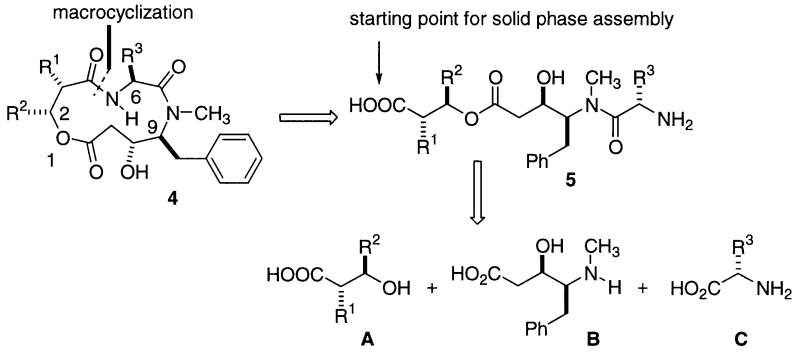


Figure 2. Design of hapalosin analogs suitable for parallel synthesis. The α-hydroxy acid is replaced by an α-amino acid.

for modifications at position 9, in the present study we restricted ourselves to the benzyl group. Another issue concerns the macrocycle bond formation. In principle, the synthesis of cyclic ring systems can be approached using various strategies,[17] such as the classical solution phase head-to-tail cyclization, the solid phase cyclorelease strategy[18] or on-support cyclization using backbone or side-chain attachment,[19] respectively. We opted for the solid phase assembly of the cyclization precursor. This approach would also allow to probe a cyclorelease macrolactamization. In the case of hapalosin, generally the amide bond is being formed. However, due to the secondary amine, the yields for the cyclization are moderate. By replacing the α-hydroxy acid with an amino acid the corresponding amide bond presents itself for the site of the final macrocyclization. At the same time, this choice determines the component that will be attached at first onto the solid phase. With an ester bond present, the final cleavage of an assembled cyclization precursor cannot be done by transesterification, but rather has to be done under acidic conditions, therefore the choice of the Wang resin. Because of the nature of the resin, the use of the boc protecting group would also not be optimal, since in the assembly process, cleavage of a boc group under strong acidic conditions could harm the Wang ester bond. Therefore, we opted for a combination of the tetrahydropyranyl- and Fmoc protective groups.

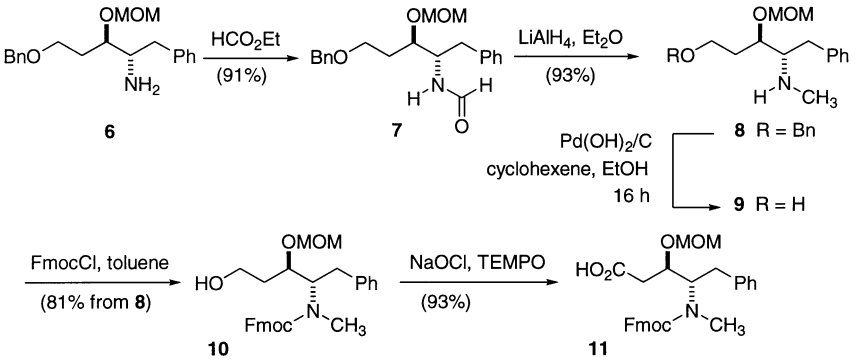
2. Results and discussion

2.1. Synthesis of the Fmoc-amino acid 11

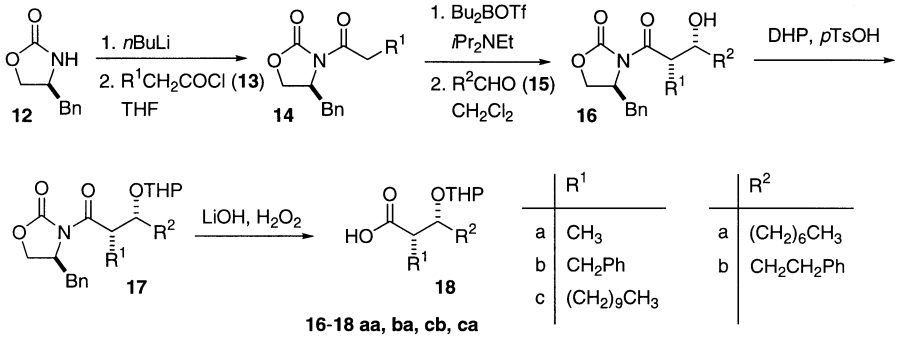
The solid-phase assembly on the Wang resin required the synthesis of the Fmoc-protected γ-amino-β-hydroxy acid **11**. This compound was prepared by branching from our previously described route (Scheme 1). Thus, the amine **6**, available via an asymmetric dihydroxylation route,[15] was converted to the formamide **7**. Hydride reduction of the amide **7** provided the *N*-methylamine **8** in good yield. After removal of the benzyl protecting group by transfer hydrogenation, treatment of the amino alcohol **9** with 9-fluorenylmethylchloroformate gave the Fmoc protected amine **10**. A final oxidation step with sodium hypochlorite delivered the desired amino acid **11**.

2.2. Synthesis of β-hydroxy acids by Evans aldol reaction

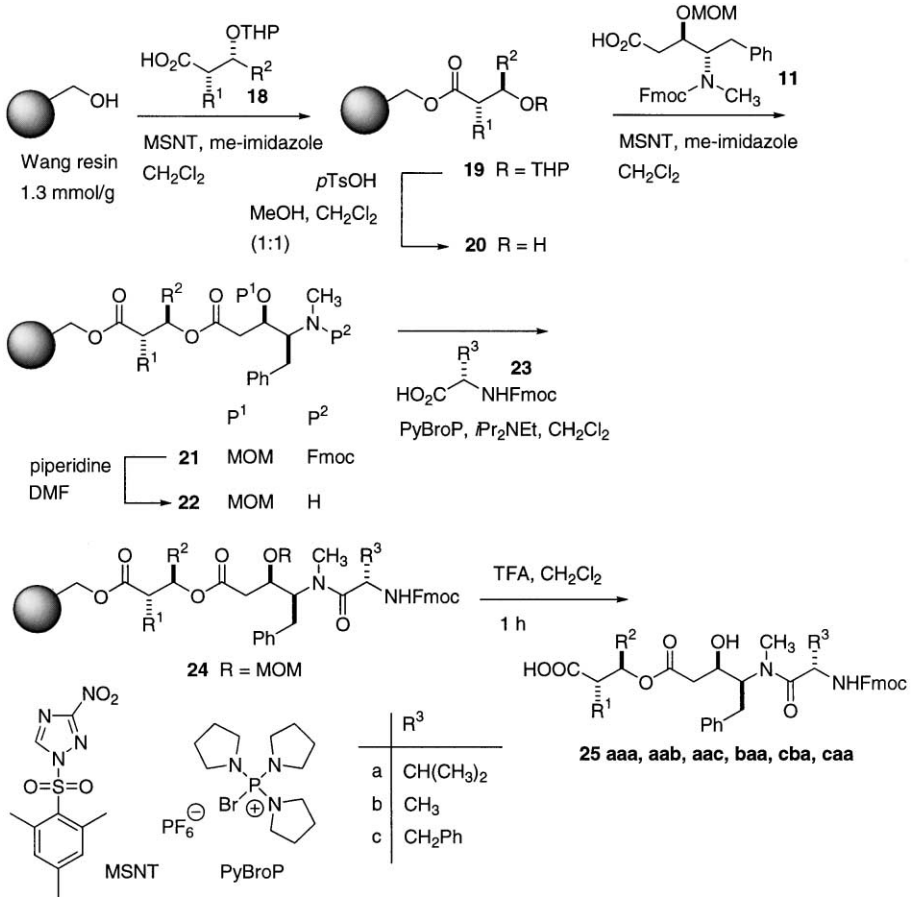
As another prelude to the solid-phase chemistry a few THP-protected β-hydroxy acids **18** were fashioned by Evans aldol reaction.[20] Starting with the known oxazolidinone **12**,[21] the sequence of deprotonation with *n*-butyllithium followed by treatment with the acid chlorides **13a** and **13b** or with the mixed anhydride of **13c** gave the acylated oxazolidinones **14a**–**14c** (Scheme 2). The chiral amide derivatives were then converted to the β-hydroxy carbonyl



Scheme 1. Synthesis of the Fmoc-protected *N*-methyl amino acid **11**.



Scheme 2. Synthesis of the THP-protected hydroxy acids **18** by Evans aldol reaction.



Scheme 3. Assembly of the acyclic depispeptide **24** by solid-phase synthesis.

compounds **18aa**, **18ba**, **18cb**, **18ca** under standard conditions. Thus, conversion of **14a**–**14c** to the corresponding boron enolates followed by addition of an aldehyde (**15a**, **15b**, respectively) and oxidative work-up gave the *syn*-aldol products **16aa**, **16ba**, **16cb**, **16ca** in high yield. The main diastereomer accounted for greater than 95% of the isolated product. Protection of the hydroxy group with dihydropyran[22] followed by removal of the chiral auxiliary under basic conditions provided the THP-protected hydroxy acids **18aa**, **18ba**, **18cb**, **18ca**. It should be noted that the Evans aldol reaction has been used recently to generate a collection of chiral 1,3-diols that were channeled into a library of tetrahydrooxazepines.[23]

2.3. Solid-phase assembly

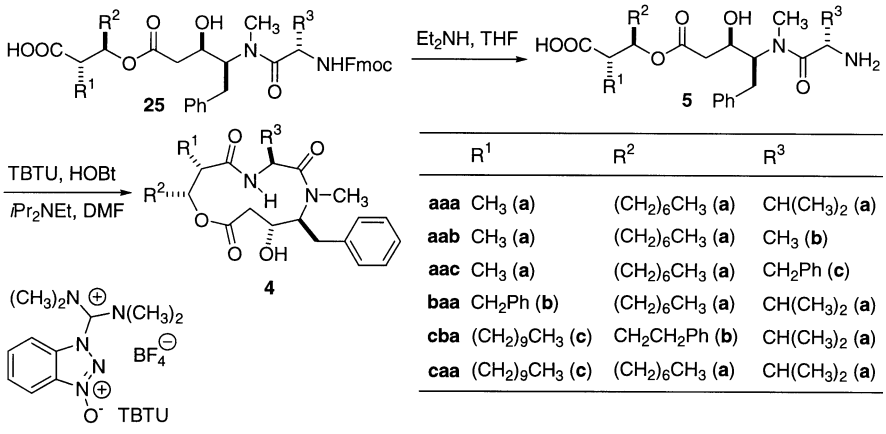
With all the building blocks in hand, we undertook the parallel synthesis of hapalosin analogs (Scheme 3). The hydroxy acids **18** were esterified with the Wang resin (capacity=1.3 mmol/g) using 1-mesitylene-2-sulfonyl)-3-nitro-1*H*-1,2,4-triazole (MSNT) in the presence of methylimidazole.[24] The acids **18aa**, **18ba**, **18cb**, **18ca** and the other reagents were used in a three-fold excess. In order to achieve good swelling of the resin, the deprotection of the THP group was done in a mixture of methanol/dichloromethane. The progress of the deprotection was monitored by GC–MS through observation of the peak at m/z=116 which corresponds to 2-methoxytetrahydro-2*H*-pyran.[25] While this method is quite efficient a chromophoric THP-derivative would be an useful alternative. The assembly was continued by adding the Fmoc-protected amino acid **11** (3 equiv.) and MSNT to the resin mixture. At this stage the loading could be estimated via monitoring the release of the Fmoc group upon addition of piperidine. It turned out that longer reaction times (30 min) caused some cleavage of the ester bond between **20** and **11**, possibly via lactam formation or β-elimination. In experiments where R^2 was a vinylic group even complete hydrolysis of the ester group occurred.

With the Fmoc group removed, an amide bond was established by reacting the *N*-methylamine **22** with Fmoc-protected α-amino acids **23a**–**c**. Knowing that the coupling of *N*-methyl amino groups is rather difficult we relied on the use of bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (PyBroP) in combination with diisopropylethylamine.[26] In some cases these couplings were run twice in order to drive them to completion. As could be judged from the deprotections of aliquots, these coupling went with high efficiency. A summary of the coupling efficiencies for all compounds and a series of steps is depicted in Table 1.

Table 1. Coupling yields for the condensation reactions yielding to the hapalosin analogs **4**

Substitution pattern	Wang resin (mmol)	Yield of resin **21** (%)[a]	Yield of resin **24** (%)[a]	Yield of amino acid **25** (%, mmol)	Yield of macrocycle **4** (%, mmol)[b]
aaa	0.10	60	100[c]	33, 0.02	60, 0.012
aab	0.20	100[d]	85[e]	82, 0.14[f]	33, 0.046
aac	0.20	100[d]	100[e]	90, 0.18[f]	44, 0.080
baa	0.20	100[d]	60[c]	30, 0.036	64, 0.023
cba	0.20	100	65[c]	21, 0.028	43, 0.012
caa	0.20	100	95[e]	53, 0.10	57, 0.057

[a] Yields were estimated spectrophotometrically by measurement of the Fmoc group, released from the resin by treatment with 20% piperidine in DMF (for details see Section 5).
[b] The yield is based on compounds **25**.
[c] Deprotection of the amino group before coupling with amino acid **23** was executed with a cleavage time of 30 min. This resulted in lower yields because of hydrolysis of the ester bound between building block **20** and **11**. In experiments where R^2 was a vinylic group complete hydrolysis of the ester group occurred.
[d] The calculation in these cases suggests a higher initial loading.
[e] Deprotection of the amino group before coupling with amino acid **23** was executed with a cleavage time of 5 min.
[f] Yield of the crude product which was used without further purification for subsequent deprotection and cyclization.



	R^1	R^2	R^3
aaa	CH_3 (**a**)	$(CH_2)_6CH_3$ (**a**)	$CH(CH_3)_2$ (**a**)
aab	CH_3 (**a**)	$(CH_2)_6CH_3$ (**a**)	CH_3 (**b**)
aac	CH_3 (**a**)	$(CH_2)_6CH_3$ (**a**)	CH_2Ph (**c**)
baa	CH_2Ph (**b**)	$(CH_2)_6CH_3$ (**a**)	$CH(CH_3)_2$ (**a**)
cba	$(CH_2)_9CH_3$ (**c**)	CH_2CH_2Ph (**b**)	$CH(CH_3)_2$ (**a**)
caa	$(CH_2)_9CH_3$ (**c**)	$(CH_2)_6CH_3$ (**a**)	$CH(CH_3)_2$ (**a**)

Scheme 4. Synthesis of the cyclization substrate **5** and the solution phase macrocyclization to the hapalosin analogs **4**.

Preliminary experiments showed that the sequence of Fmoc deprotection and acid treatment resulting in the amino acid **5aaa** is not optimal since this amino acid is difficult to purify by chromatography. Unfortunately, the Fmoc deprotection did not lead to cleavage from the resin in a cyclorelease amide formation. Therefore, cleavage from the resin was done prior to the removal of the Fmoc protecting group. Under the conditions used (TFA/CH_2Cl_2) the MOM protecting group was also cleaved. The Fmoc-protected amino acids **25** proved to be quite pure, thus demonstrating the efficiency of the solid-phase assembly. They were characterized by NMR spectroscopy and mass spectrometry. After chromatographic purification, treatment of the amino acids **25** with diethylamine in THF followed by concentration in vacuo to remove the fluorenylamine adduct gave the amino acids **5** (Scheme 4).

The crucial macrocyclization reactions were run under high dilution (c=1 mmol/l) in DMF as solvent and 2-(1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate as condensing agent. Gratifyingly, the macrolactamization reaction proved to be quite efficient, with yields for the macrocycles **4** ranging from 33 to 64%. The structures for the hapalosin analogs were secured by high resolution mass spectra and by NMR spectrometry. In one instance (**4aaa**) the conformational situation in the macrocyclic ring was further examined by homo- and heteronuclear NMR methods.

3. Conformational studies

Due to isomerism about the tertiary amide bond hapalosin (**3**) exists at room temperature as a mixture of *s-cis* and *s-trans* rotamer which leads to a doubled signal set in NMR spectra. The *cis* rotamer is the dominating conformer in $CDCl_3$ (*cis*/*trans* 3:1)[12] while it is the minor conformer in DMSO-d_6 (*cis*/*trans* 1:3).[16] The hapalosin analog **4aaa** shows two signal sets, both in the ^{1}H and ^{13}C NMR spectra. However, the ratio suggests a stronger preference of one conformer (93:7 in DMSO-d_6). The corresponding peak assignments are shown in Table 2.

To elucidate the solution conformation of the analog **4aaa**, homo- and heteronuclear NMR spectra were measured in DMSO-d_6. Compensated ROESY[27] spectra (O1=2.1 ppm, 4 kHz pulsed spin lock, 200 ms mixing time) show an intense NOE correlation between H-6 and H-9, which proves the *s-cis*-conformation of the tertiary amide bond. Table 3 contains the average interproton distances (Å) obtained from the cross signal intensities in the ROESY spectrum of **4aaa**. Under the experimental conditions spin diffusion is neglectable and the volume integral of each cross-peak correlates with a single interproton distance (two-spin approximation).[28] The proton–proton distances were calculated according to the r^{-6}-dependance (r=interproton distance) of the NOE.[29] The NOE distances served as weak distance restraints for a 100 ps molecular dynamics simulation. Additional weak torsional restraints were included for the benzylic side chain and the C10–C11 bond. Averaging of 10 snapshots was followed by energy minimization without distance constraints. Interproton distances of this average conformation of **4aaa** are listed in the column MD distance of Table 3.

Table 2. Peak assignments for the ^{1}H and ^{13}C NMR spectra of **4aaa** measured in DMSO-d_6

C/H-number	^{13}C shift	^{1}H shift
2	75.29	4.816
3	40.45	2.834
5	–	8.079
6	53.43	3.471
9	59.67	3.924
10	69.53	3.962
11	40.06	2.601 ($H^{Pro S}$)
		2.391 ($H^{Pro R}$)
13	27.34	2.022+1.506
14	25.12	1.398+1.137
15–18	22.08	1.265
	28.42	1.265
	31.17	1.250
19	13.92	0.857
20	12.52	0.935
22	19.05	0.124
23	18.01	0.473
24	28.41	2.790
25	33.28	3.021 ($H^{Pro S}$)
		2.681 ($H^{Pro R}$)
4/7/12	171.82	
C=O	170.17	
	169.65	
10-OH	–	5.244

The prochiral assignments of the diastereotopic methylene groups CH_2-11 and CH_2-25 are based on the combined data of the NOE intensities and the $^3J_{H,H}$ coupling constants. For methylene group CH_2-11 NOE correlations were observed on the one hand between H-11$^{Pro S}$ and H-9 (distance <3 Å) and on the other hand between H-11$^{Pro R}$ and O*H* (distance <3 Å). Coupling constants indicate an antiperiplanar orientation of H-11$^{Pro S}$ and H-10 ($^3J_{H11,H10}$=10.1 Hz) and a synclinal orientation of H-11$^{Pro R}$ and H-10 ($^3J_{H11,H10}$<2 Hz). In the case of the benzylic methylene group CH_2-25, NOE correlations were found between H-25$^{Pro S}$ and H-9 (~2.5 Å) and also between H-25$^{Pro S}$ and H-10 (distance <3 Å). The proton H-25$^{Pro R}$ exhibits correlations to H-9 (distance ~3 Å), H-10 (distance >3 Å) and H_3-24 (distance <3 Å). Coupling constants indicate an antiperiplanar orientation of

Table 3. Experimental interproton distances (Å) obtained from a compensated ROESY spectrum and the corresponding theoretical results from molecular dynamics simulation of **4aaa**. The torsional restraints for the MD simulation are listed above

H–H	NOE distance	MD distance
5–3	2.05	2.24
5–6	2.95	3.00
5–9	3.1	3.16
5–10	3.5	3.68
5–21	2.9	2.85
2–3	2.2	2.35
6–9	2.1	2.10
Torsion	(°)	
C6–C(O)—N–C9	0	
H9–C9–C25—H25$^{pro R}$	180	
H9–C9–C25—H25$^{pro S}$	−60	
H10–C10–C11–H11$^{pro R}$	−60	
H10–C10–C11–H11$^{pro S}$	180	

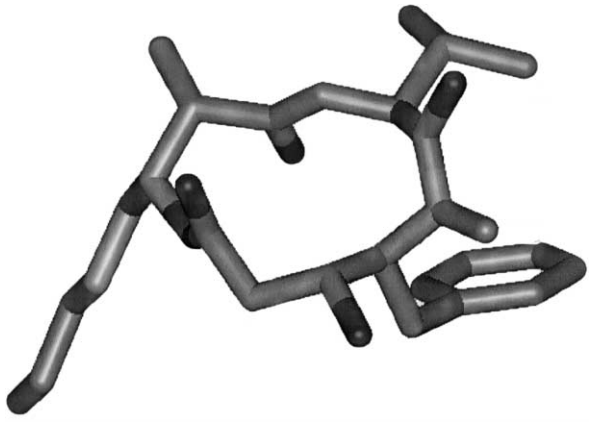


Figure 3. Energy-minimized average conformations of **4aaa** (*cis*-conformer). To simplify the calculation, the side-chain was shortened by two atoms.

H-25$^{Pro\mathit{R}}$ and H-9 ($^3J_{H25,H9}$=11 Hz) and a synclinal orientation of H-25$^{Pro\mathit{S}}$ and H-9 ($^3J_{H25,H9}$=2.5 Hz). The averaged and energy-minimized conformation of **4aaa** that is shown in Fig. 3 fulfills all NOE data.

As determined in a previous study, the *cis*/*trans* ratio for hapalosin in the same solvent was 25:75.[16] Thus, the replacement of an ester- with an amide bond seems to enhance the *cis*/*trans*-ratio.

4. Conclusion

In this paper we illustrate the synthesis of a small library of analogs of the depsipeptide hapalosin. The analogs are characterized by one ester and two amide bonds. The three building blocks consist of β-hydroxy acids **18**, α-amino acids **23** and the unusual γ-amino-β-hydroxy acid **11**. As protecting groups the Fmoc for the amino function, and the THP-group for the hydroxy function proved to be advantageous. With a view towards generating structural variability the aldol reaction holds great potential. The corresponding building blocks, carboxylic acids and aldehydes are available in large number. In addition, the aldol products can be converted to many interesting building blocks, for example to 1,2-amino alcohols by Curtius rearrangement. We believe that the general strategy outlined here should work as well for other depsipeptides. Studies along these lines are underway in our laboratory.

5. Experimental

5.1. General

^{1}H and ^{13}C NMR: Bruker AC 250, Bruker AMX 400, Bruker DRX 600; all spectra were recorded in $CDCl_3$ unless noted otherwise; chemical shifts are calibrated to residual proton resonances in $CDCl_3$ (7.24 ppm) and DMSO-d_6 (2.49 ppm), respectively. Optical rotations: JASCO P-1020 polarimeter. IR: Jasco FT/IR-430 spectrometer. UV: Shimadzu 240-1PC UV–VIS recording spectrophotometer. GC–MS: HP 6890 Series GC System with 5973 mass selective detector and 7683 Series injector. EI-MS: AMD Intectra GmbH AMD 402. ES-FT-ICR-MS: Bruker Daltonic APEX II. HPLC: Hewlett Packard HP 1100. Flash chromatography: J. T. Baker silica gel 30–60 μm. Thin-layer chromatography: Merck Si 60 F_{254}. Solvents were distilled prior to use; petroleum ether with a boiling range 35–65°C was used. The following compounds were prepared according to literature procedures: 2-amino-5-*O*-benzyl-1,2,4-trideoxy-3-*O*-(methoxymethyl)-1-phenyl-D-threo-pentitol (**6**),[15] (4*S*)-4-benzyl-3-propionyl-1,3-oxazolidin-2-one (**12**),[21] (*S*)-4-benzyl-3-propionyl-2-oxazolidinone (**14a**),[21] (*S*)-4-benzyl-3-(3-phenylpropionyl)-2-oxazolidinone (**14b**)[30]. Manual assembling of the linear depsipeptides was performed in a polypropylene column (isolute SPE column from Roland Vetter, Germany) fitted with a porous polyethylene frit (20 μm porosity) using an IKA Vibrax-VXR for agitation. Wang resin (100–200 mesh, loading capacity 1.3 mmol/g), the condensation reagents PyBroP and TBTU and the Fmoc protected amino acids were purchased from Novabiochem.

5.1.1. 5-*O*-Benzyl-1,2,4-trideoxy-2-(*N*-formylamino)-3-*O*-(methoxymethyl)-1-phenyl-*erythro*-D-pentitol (7). A solution of amine **6** (3.45 g, 10.5 mmol) in ethyl formate (20 ml) was heated at reflux for 26 h. After removal of the excess ethyl formate under reduced pressure, the residue was purified by flash chromatography (20% petroleum ether in ethyl acetate) to give formamide **7** (3.43 g, 91%) as a light yellow oil. $[\alpha]^{25}_D$=−29.1 (*c* 0.8, CH_2Cl_2); TLC (petroleum ether/ethyl acetate, 2:8): R_f=0.46; IR (neat): 3291 (m), 1687 (s) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$): δ (both rotamers)=1.82–1.93 (m, 2H, CH_2), 2.58 (dd, *J*=10.6, 14.2 Hz, 1H, minor, CH_2Ph), 2.70 (dd, *J*=9.5, 14.2 Hz, 1H, major, CH_2Ph), 2.88–2.99 (m (∼2×dd, *J*=5.2, 14.2 Hz), 1H, CH_2Ph), 3.39, 3.40 (s, 3H, OCH_3), 3.54–3.64 (m, >2H, CH_2OBn, CHN (minor)), 3.76–3.82 (m, 1H, CHOMOM), 4.44–4.51 (m, <3H, OCH_2Ph, CHN (major)), 4.57–4.68 (m (∼2×d, *J*=6.9 Hz), 2H, CH_2OMe), 6.48 (d, br., 1H, minor, NH), 6.55 (d, br., 1H, major, NH), 7.03–7.07 (m, <1H, aryl H), 7.14–7.37 (m, >9H, aryl H), 7.47 (d, *J*=11.8 Hz, 1H, minor, CHO), 7.98 (d, *J*=1.3 Hz, 1H, major, CHO); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ (both rotamers)=31.7, 32.4, 35.5, 36.7, 51.4, 55.9, 57.6, 66.1, 66.4, 73.2, 73.3, 79.6, 79.9, 97.5, 97.7, 126.4, 126.7, 127.7, 127.9, 128.0, 128.4, 128.5, 128.7, 129.2, 129.4, 137.7, 138.0, 138.1, 138.2, 160.5, 164.2.

5.1.2. 5-*O*-Benzyl-1,2,4-trideoxy-3-*O*-(methoxymethyl)-2-(*N*-methylamino)-1-phenyl-*erythro*-D-pentitol (8). A solution of formamide **7** (3.4 g, 9.5 mmol) in diethyl ether (30 ml) was added dropwise at room temperature to a stirred suspension of $LiAlH_4$ (0.72 g, 19.0 mmol) in dry diethyl ether (100 ml). The reaction mixture was stirred at reflux for 24 h and then cooled in an ice bath. Water (120 ml) was added carefully to destroy the excess of $LiAlH_4$ followed by the addition of diethyl ether (70 ml). The layers were separated and the aqueous layer was extracted with Et_2O (3×150 ml). The combined organic layers were washed with brine (150 ml), dried ($MgSO_4$), filtered and concentrated in vacuo to give crude the amine **8** (3.05 g, 93%) as a yellow oil which was used in the next step without further purification. $[\alpha]^{25}_D$=+24.4 (*c* 0.54, CH_2Cl_2); TLC (ethyl acetate/MeOH, 8:2): R_f=0.29–0.34; ^{1}H NMR (250 MHz, $CDCl_3$): δ=1.58 (s, br., 1H, NH), 1.80–1.88 (m, 2H, CH_2), 2.31 (s, 3H, NCH_3), 2.63–2.66 (m, 2H, CHN,

CH_2Ph), 2.77–2.83 (m, 1H, CH_2Ph), 3.26 (s, 3H, OCH_3), 3.44–3.57 (m, 2H, CH_2OBn), 3.69–3.76 (m, 1H, CHOMOM), 4.47, 4.52 (2 d, J=12.0 Hz, 2H, OCH_2Ph), 4.49, 4.58 (2 d, J=6.7 Hz, 2H, CH_2OMe), 7.06–7.27 (m, 10H, aryl H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=30.7, 35.1, 36.7, 55.7, 64.6, 67.2, 73.0, 76.3, 96.9, 126.2, 127.6, 127.7, 128.4, 128.5, 129.2, 138.6, 139.6; MS (EI), *m/z* (%) 344 [M^++1] (1.8).

5.1.3. 1,2,4-Trideoxy-2-(*N*-methylamino)-3-*O*-(methoxymethyl)-1-phenyl-*erythro*-D-pentitol (9). A solution of crude benzyl ether **8** (0.8 g, 2.3 mmol) in EtOH/cyclohexene 2:1 (15 ml) was stirred in the presence of $Pd(OH)_2$ (0.2 g) at reflux for 16 h. The reaction mixture was filtered through a pad of Celite, and the filtrate evaporated in vacuo to leave the crude amino alcohol **9** as a yellow oil which was used directly in the subsequent step. ^1H NMR (250 MHz, $CDCl_3$): δ=1.75–1.87, 1.92–1.97 (2 m, 2H, CH_2), 2.42 (s, 3H, NCH_3), 2.72 (dd, J=7.5, 13.9 Hz, 1H, CH_2Ph), 2.86 (dd, J=7.2, 13.9 Hz, 1H, CH_2Ph), 2.99–3.07 (m, 1H, CHN), 3.34 (s, 3H, OCH_3), 3.53–3.60 (m, 1H, CHOMOM), 3.69–3.79 (m, 2H, CH_2OH), 4.58, 4.62 (d, J=6.8 Hz, 2H, CH_2OMe), 7.17–7.33 (m, 5H, aryl H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=32.8, 34.5, 36.2, 55.7, 57.1, 63.5, 77.4, 95.9, 126.5, 128.7, 129.0, 138.5.

5.1.4. 1,2,4-Trideoxy-2-[*N*-(9-fluorenylmethoxycarbonyl)-*N*-methylamino]-3-*O*-(methoxymethyl)-1-phenyl-*erythro*-D-pentitol (10). To a cooled (0°C) solution of FmocCl (0.78 g, 3.0 mmol) in toluene (30 ml) was added dropwise a solution of the crude amino alcohol **9** (2.3 mmol) in toluene (20 ml) followed by the addition of saturated aqueous $NaHCO_3$ (10 ml). The resulting mixture was vigorously stirred at 0°C for 20 min and for 1 h at room temperature. Water (20 ml) was added and the layers were separated. After extraction of the water layer with ethyl acetate (40 ml), the organic layers were combined, washed with brine (40 ml), dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification of the residue by flash chromatography (30% petroleum ether in ethyl acetate) gave **10** (0.89 g, 81%). $[\alpha]^{26}_D$=−18.7 (*c* 0.18, CH_2Cl_2); TLC (ethyl acetate/petroleum ether, 6:4): R_f=0.22; IR (neat): 3461 (m), 1695 (s) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ (both rotamers)=1.17–1.31, 1.40–1.56 (2 m, br., 2H, minor, CH_2), 1.60–1.69, 1.79–1.87 (2 m, 2H, major, CH_2), 2.45–2.65 (m, br.) and 2.61 (s, 3H, NCH_3), 2.78–2.92 (m, 1H, CH_2Ph), 3.18 (dd, J=4.1, 14.4 Hz, 1H, CH_2Ph), 3.39, 3.44 (s, 3H, OCH_3), 3.40–3.68 (m, 2H, minor, CH_2OH), 3.72–3.82 (m, 2H, major, CH_2OH), 3.90–4.01 (m, <1H, CHOMOM), 4.03–4.15 (m, <2H, CHN, CH(Fmoc)), 4.21 (dd, J=7.1, 10.5 Hz, 1H, CH_2(Fmoc)), 4.35 (dd, J=6.5, 10.5 Hz, CH_2(Fmoc)), 4.3–4.45, 4.46–4.59 (2 m, br., minor, CH_2OMe), 4.71, 4.75 (2 d, J=6.7 Hz, major, CH_2OMe), 6.7–6.85 (m, <1H, aryl H), 7.10–7.58 (m, 10H, aryl H), 7.70–7.83 (m, >2H, aryl H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ (both rotamers)=34.0, 34.3, 47.3, 56.3, 58.9, 59.0, 67.2, 78.3, 97.6, 97.8, 119.9, 120.1, 124.5, 125.0, 125.1, 126.2, 126.4, 127.0, 127.2, 127.7, 128.4, 128.5, 128.8, 138.4, 141.3, 141.4, 141.6, 142.8, 144.2, 144.3, 155.2, 156.6; MS (FD), *m/z* (%) 474.7 [M^+-1] (100).

5.1.5. (3*R*,4*S*)-4-[*N*-(9-Fluorenylmethoxycarbonyl)-*N*-methylamino]-3-(methoxymethoxy)-5-phenylpentanoic acid (11). To a stirred heterogeneous mixture of **10** (0.85 g, 1.8 mmol), acetone (14 ml) and aqueous 5% $NaHCO_3$ (5 ml) were added KBr (0.21 g, 0.18 mmol) and TEMPO (0.29 g, 1.86 mmol) at 0°C. An aqueous NaOCl solution (~1.9 M, 5.5 ml, ~10.5 mmol) was then added dropwise, while the mixture was vigorously stirred at 0°C. After 1 h additional NaOCl (2 ml, ~3.8 mmol) was added, and stirring was continued at 0°C for another hour followed by the addition of saturated aqueous $NaHCO_3$ (35 ml). The acetone was then removed in vacuo, and the resulting aqueous mixture extracted with diethyl ether (2×30 ml) to remove TEMPO impurities and then acidified to pH 5–6 with 10% aqueous citric acid. After extraction of the aqueous layer with ethyl acetate (3×60 ml) the combined ethyl acetate layers were dried ($MgSO_4$), filtered and concentrated in vacuo to give the pure acid **11** (0.82 g, 93%). $[\alpha]^{28}_D$=−46.2 (*c* 0.64, CH_2Cl_2); TLC (ethyl acetate/petroleum ether, 8:2): R_f=0.20–0.23; IR (neat): 3600–2500 (br), 1736 (s), 1703 (s) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ (both rotamers)=2.06–2.15 (m, 1H, CH_2CO), 2.4–2.68 (m, 4H, CH_2O, NCH_3), 2.79–2.95 (m, <1H, CH_2Ph), 3.22–3.28 (m, <1H, CH_2Ph), 3.33, 3.40 (2 s, 3H, OCH_3), 4.06–4.15 (m, <2H, CH, CH(Fmoc)), 4.22–4.40 (m, <3H, CH, CH_2(Fmoc)), 4.39–4.66 (m, br., <1H, CH_2OMe), 4.70, 4.77 (2 d, J=6.8 Hz, 1H, CH_2OMe), 6.75 (s, br., <1H, aryl H), 7.10–7.53 (m, 10H, aryl H), 7.69–7.78 (m, 2H, aryl H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ (both rotamers)=34.4, 38.0, 47.3, 56.0, 56.2, 67.3, 97.2, 119.9, 120.2, 124.5, 125.1, 126.3, 126.5, 127.0, 127.1, 127.3, 127.6, 127.7, 128.4, 128.5, 128.8, 128.9, 138.4, 141.3, 141.4, 141.5, 143.8, 144.0, 144.3, 156.3, 156.6, 175.6, 175.8; MS (FD), *m/z* (%) 488.8 [M^+−1] (100).

5.1.6. (4*S*)-4-Benzyl-3-dodecanoyl-2-oxazolidinone (14c). A stirred solution of dodecanoic acid (2.60 g, 13.1 mmol) in dry THF (60 ml) was treated with Et_3N (3.6 ml, 26.1 mmol) and pivaloyl chloride (1.7 g, 14.1 mmol) at −15°C. After warming slowly to 0°C, the resulting mixture was cooled to −78°C. In a separate flask, a solution of auxiliary **12** (2.50 g, 14.1 mmol) in dry THF (40 ml) was treated with *n*-BuLi (2.7 M in heptane, 5.3 ml, 14.3 mmol) at −78°C. The solution of the lithiated oxazolidinone was stirred at −78°C for 10 min before it was transferred to the cooled (−78°C) reaction mixture of the mixed anhydride. The resulting mixture was allowed to warm to −20°C within 1 h and stirred at this temperature for 30 min. After addition of aqueous $NaHSO_4$ (1 M, 40 ml), the bulk of THF was removed by rotary evaporation, and the remainder extracted with ethyl acetate (2×60 ml). The combined organic layers were washed with 5% aqueous Na_2CO_3 and brine, dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was purified by flash chromatography (10 and 20% ethyl acetate in petroleum ether) to give **14c** (4.64 g, 99%) as a colorless crystalline solid. mp 47°C; TLC (petroleum ether/ethyl acetate, 8:2): R_f=0.60; ^1H NMR (250 MHz, $CDCl_3$): δ=0.87 (t, J=6.4 Hz, 3H, CH_3), 1.22–1.40 (m, 16H), 1.62–1.71 (m, 2H), 2.76 (dd, J=9.6, 13.3 Hz, 1H, CH_2Ph), 2.81–3.03 (m, 2H, $CH_2C(O)$), 3.29 (dd, J=3.3, 13.3 Hz, 1H, CH_2Ph), 4.11–4.23 (m, 2H, CH_2O), 4.62–4.71 (m, 1H, CHN), 7.18–7.36 (m, 5H, aryl H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=14.1, 22.7, 24.3, 29.2, 29.4, 29.5, 29.7, 31.9, 35.6, 38.0, 55.2, 66.2, 127.4, 129.0, 129.5, 135.4, 153.5, 173.5.

5.2. Preparation of the aldol products 16aa, 16ba, 16cb, 16ca

To a stirred solution of the oxazolidinone **14** in dry CH_2Cl_2 (0.5 M) was added *n*-Bu_2BOTf (1 M in CH_2Cl_2, 1.3 equiv.) dropwise at 0°C followed by the dropwise addition of diisopropylethylamine (1.3 equiv.). After stirring for 1 h at 0°C, the solution was cooled to −78°C, and the aldehyde **15** (1.4 equiv.) was added at this temperature. The resulting mixture was stirred for 1 h at −78°C, then allowed to warm to room temperature in 1 h and kept at room temperature for 2 h. After quenching the reaction with phosphate buffer (pH 7.0, 3 ml/mmol of **14**), the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2×). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and evaporated in vacuo to leave an oil which was dissolved in MeOH (3 ml/mmol **14**). After cooling to 0°C, the solution was treated dropwise with 30% aqueous H_2O_2 (1 ml/mmol of **14**) and stirred for 1 h at 0°C. The reaction was quenched by the addition of 10% aqueous $NaHSO_4$ (same volume as MeOH), and after warming to room temperature, the resulting mixture was extracted with ethyl acetate (3×). The ethyl acetate layers were combined, washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), filtered and concentrated in vacuo. Purification of the residue by flash chromatography gave the pure aldol product **16** as a colorless oil.

5.2.1. (4*S*)-4-Benzyl-3-[(2*S*,3*R*)-3-hydroxy-2-methyldecanoyl]-2-oxazolidinone (16aa). Eluents for flash chromatography: 20 and 30% ethyl acetate in petroleum ether, yield: 80%. $[\alpha]^{21}_D$=+42.6 (*c* 1.4, $CHCl_3$); TLC (petroleum ether/ethyl acetate, 7:3): R_f=0.44; ^{1}H NMR (250 MHz, $CDCl_3$): δ=0.87 (m, 3H, CH_3), 1.2–1.6 (m, 15H, $(CH_2)_6$, CH_3), 2.44 (s, br., 1H, OH), 2.78 (dd, *J*=9.4, 13.4 Hz, 1H, CH_2Ph), 3.24 (dd, *J*=3.3, 13.4 Hz, 1H, CH_2Ph), 3.75 (dq, *J*=2.7, 7.0 Hz, 1H, CHMe), 3.90–3.95 (m, 1H, CHOH), 4.15–4.26 (m, 2H, CH_2O), 4.65–4.73 (m, 1H, CHN), 7.17–7.21, 7.23–7.36 (m, 5H, aryl H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=10.4, 14.1, 22.7, 26.1, 29.3, 29.6, 31.9, 33.9, 34.9, 37.9, 42.1, 55.2, 66.2, 71.5, 127.5, 129.0, 129.5, 135.1, 153.1, 177.6; HRMS (EI): calcd for $C_{21}H_{31}NO_4$ 361.22529, found 361.22922.

5.2.2. (4*S*)-4-Benzyl-3-[(2*S*,3*R*)-2-benzyl-3-hydroxydecanoyl]-2-oxazolidinone (16ba). Eluents for flash chromatography: 20 and 30% ethyl acetate in petroleum ether, yield: 81%. $[\alpha]^{25}_D$=+36.9 (*c* 0.976, CH_2Cl_2); TLC (petroleum ether/ethyl acetate, 7:3): R_f=0.51; ^{1}H NMR (250 MHz, $CDCl_3$): δ=0.88 (m, 3H, CH_3), 1.22–1.40 (m, 10H), 1.45–1.66 (m, 2H), 2.17 (dd, *J*=9.4, 13.5 Hz, 1H, CH_2Ph(auxiliary)), 2.84 (dd, *J*=3.2, 13.5 Hz, 1H, CH_2Ph(auxiliary)), 3.03 (dd, *J*=5.2, 13.4 Hz, 1H, CH_2Ph), 3.14 (dd, *J*=10.5, 13.4 Hz, 1H, CH_2Ph), 3.91–4.01 (m, 1H, CH), 3.98 (dd, *J*=3.0, 9.1 Hz, 1H, CH_2O), 4.07 (dd, *J*=7.8, 9.1 Hz, 1H, CH_2O), 4.52–4.65 (m, 2H, CHN, CH), 6.91–6.94 (m, 2H, aryl H), 7.16–7.28 (m, 8H, aryl H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=14.1, 22.7, 26.1, 29.3, 29.5, 31.9, 33.1, 34.0, 37.3, 49.3, 55.0, 65.7, 72.5, 126.5, 127.3, 128.5, 128.9, 129.3, 129.5, 135.1, 138.8, 153.4, 175.2.

5.2.3. (4*S*)-4-Benzyl-3-{(2*S*)-2-[(1*R*)-1-hydroxy-3-phenylpropyl]dodecanoyl}-2-oxazolidinone (16cb). Eluent for flash chromatography: 20% ethyl acetate in petroleum ether, yield: 92%. TLC (petroleum ether/ethyl acetate, 8:2): R_f=0.38; ^{1}H NMR (250 MHz, $CDCl_3$): δ=0.86 (m, 3H, CH_3), 1.16–1.35 (m, 16H, $(CH_2)_8$), 1.50–1.70 (m, 1H, CH_2), 1.7–1.96 (m, 3H, CH_2, CH_2Bn), 2.59–2.73 (m, 2H, CH_2Ph(auxiliary), CH_2Ph), 2.78–2.96 (m, 1H, CH_2Ph), 3.34 (dd, *J*=3.2, 13.2 Hz, 1H, CH_2Ph(auxiliary)), 3.85–3.92 (m, 1H, CH), 4.04–4.10, 4.10–4.19 (m, 3H, CH, CH_2O), 4.68–4.74 (m, 1H, CHN), 7.14–7.37 (m, 10H, aryl H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=14.1, 22.7, 27.3, 27.6, 29.3, 29.4, 29.6, 29.8, 31.9, 32.3, 35.4, 38.1, 47.8, 55.6, 66.0, 71.8, 125.9, 127.4, 128.4, 128.5, 129.0, 129.4, 135.2, 141.9, 153.7, 176.1.

5.2.4. (4*S*)-4-Benzyl-3-{(2*S*)-2-[(1*R*)-1-hydroxyoctyl]dodecanoyl}-2-oxazolidinone (16ca). Eluents for flash chromatography: 10, 15 and 20% ethyl acetate in petroleum ether, yield: 88%. TLC (petroleum ether/ethyl acetate, 8:2): R_f=0.37; ^{1}H NMR (250 MHz, $CDCl_3$): δ=0.83–0.88 (m, 6H, 2×CH_3), 1.2–1.4 (m, 26H, $(CH_2)_8$, $(CH_2)_5$), 1.42–1.55 (m, 2H, CH_2), 1.50–1.70, 1.78–1.96, (2 m, 2H, CH_2), 2.69 (dd, *J*=10.0, 13.2 Hz, 1H, CH_2Ph), 3.35 (dd, *J*=3.3, 13.2 Hz, 1H, CH_2Ph), 3.84–3.89 (m, 1H, CH), 4.02–4.07 (m, 1H, CH), 4.13–4.22 (m, 2H, CH_2O), 4.67–4.77 (m, 1H, CHN), 7.21–7.37 (m, 5H, aryl H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=14.1, 22.7, 26.2, 27.0, 27.6, 29.3, 29.4, 29.5, 29.6, 29.9, 31.9, 33.9, 38.1, 47.8, 55.6, 66.0, 72.6, 127.4, 129.0, 129.4, 135.3, 153.6, 176.2.

5.3. Preparation of the THP protected β-hydroxy acids 18aa, 18ba, 18cb, 18ca

After addition of pyridinium *para*-toluenesulfonate (PPTS, 0.1 equiv.) to a solution of β-hydroxy compound **16** and 3,4-dihydro-2*H*-pyran (1.5 equiv.) in dry CH_2Cl_2 (0.15 M), the resulting solution was stirred for 12 h at room temperature. The reaction solution was diluted with CH_2Cl_2 and then washed once with half-saturated brine to remove PPTS. After drying ($MgSO_4$) and filtration, the CH_2Cl_2 solution was evaporated in vacuo to leave the crude product **17** as a light yellow oil which was used as such in the subsequent cleavage of the auxiliary.

The crude product **17** was dissolved in THF/H_2O 3:1 (0.05 M) and cooled to 0°C. To the cooled and stirred solution was added dropwise 30% aqueous H_2O_2 (0.6 ml/mmol, ~6 equiv.) followed by the addition of LiOH monohydrate (2 equiv.). The resulting mixture was stirred for 20 min at 0°C and then at room temperature for 8 h. After quenching with aqueous Na_2SO_3 (1.5 M, 7 ml/ml H_2O_2) at 0°C, most of the THF was removed under reduced pressure. The remainder was diluted with CH_2Cl_2 before acidifying the cooled (0°C) mixture to pH 6 with aqueous 1N HCl. The layers were separated, and after extraction of the aqueous layer with CH_2Cl_2 (2×), the organic layers were combined, washed with aqueous HCl (1N) and brine, dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was purified by flash chromatography to give the product **18** as a colorless oil.

5.3.1. (2*S*,3*R*)-2-Methyl-3-(tetrahydropyran-2-yloxy)decanoic acid (18aa). Eluent for flash chromatography: 35% ethyl acetate in petroleum ether, yield: 93%. $[\alpha]^{23}_D$=+44.7

(*c* 1.2, $CHCl_3$); TLC (petroleum ether/ethyl acetate, 6:4): R_f=0.52; IR (neat): 3400–2650 (br), 1709 (s) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ (both diastereomers)=0.86 (t, *J*=6.8 Hz, 3H, CH_3), 1.14, 1.16 (d, *J*=3.1 Hz, 3H, Me), 1.2–1.38 (m, 10H, $(CH_2)_5$), 1.40–1.90 (m, 8H, CH_2, $(CH_2)_3$(THP)), 2.65–2.73, 2.83–2.89 (m, 1H, CHMe), 3.45–3.53 (m, 1H, CH_2O), 3.77–3.96 (m, 2H, CHOTHP, CH_2O), 4.60–4.65, 4.68–4.72, 4.91–4.97 (m, 1H, CH(THP)); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ (both diastereomers)=11.2, 12.1, 14.0, 19.8, 20.5, 22.6, 25.4, 25.5, 25.7, 26.0, 29.2, 29.5, 29.6, 30.7, 30.8, 30.9, 31.2, 31.8, 32.5, 42.2, 43.6, 62.9, 64.1, 78.6, 79.9, 94.7, 98.8, 100.4, 176.9, 178.9; MS (EI), *m/z* (%) 287 (16) [M^++1], 203 (30), 185 (46), 101 (77), 85 (100).

5.3.2. (2*S*,3*R*)-2-Benzyl-3-(tetrahydropyran-2-yloxy)decanoic acid (18ba). Eluent for flash chromatography: 25% ethyl acetate in petroleum ether, yield: 64%. $[\alpha]^{25}_D$=+61.3 (*c* 1.10, CH_2Cl_2); TLC (petroleum ether/ethyl acetate, 7:3): R_f=0.66; IR (neat): 3450–2600 (br), 1708 (s) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ (both diastereomers)=0.88 (m, 3H, CH_3), 1.2–1.4 (m, 10H, $(CH_2)_5$), 1.4–1.9 (m, 8H, CH_2, $(CH_2)_3$(THP)), 2.73–2.87, 2.93–3.09, 3.14–3.21 (m, 3H, CHBn, CH_2Ph), 3.42–3.58, 3.71–3.79, 3.81–4.0 (m, 3H, CH_2O, CHOTHP), 4.51–4.54, 4.70–4.75, 4.90–4.98 (m, 1H, CH(THP)), 7.16–7.30 (m, 5H, aryl H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ (both diastereomers)=14.1, 19.4, 20.7, 22.7, 25.1, 25.4, 25.5, 25.6, 25.7, 25.9, 29.2, 29.4, 29.6, 30.7, 31.2, 31.8, 32.3, 33.0, 33.5, 34.0, 50.4, 51.6, 52.9, 62.9, 64.5, 71.9, 79.3, 94.7, 98.2, 100.9, 126.3, 126.4, 128.5, 128.7, 128.8, 139.2, 139.5, 175.8, 177.8, 178.8; MS (FAB), *m/z* (%) 363 (20) [M+1], 279 (100), 261 (63), 243 (45), 215 (38).

5.3.3. (2*R*)-2-[(1*S*)-3-Phenyl-1-(tetrahydro-2*H*-pyran-2-yloxy)propyl]dodecanoic acid (18cb). Eluent for flash chromatography: 20% ethyl acetate in petroleum ether, yield: 87%. TLC (petroleum ether/ethyl acetate, 7:3): R_f=0.56; IR (neat): 3500–2500 (br), 1783 (m), 1709 (s), 1666 (m) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ (both diastereomers)=0.85–0.87 (m, 3H, CH_3), 1.2–1.4 (m, 16H, $(CH_2)_8$), 1.48–1.98 (m, 10H, CH_2, $(CH_2)_3$(THP), CH_2Bn), 2.46–2.98 (m, 3H, CH_2Ph, CHC(O)), 3.45–3.6, 3.68–3.75, 3.8–4.1 (m, 3H, CH_2O, CHOTHP), 4.54–4.60, 4.71–4.77, 4.92–4.98 (m, 1H, CH(THP)), 7.1–7.3 (m, 5H, aryl H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ (both diastereomers)=14.1, 19.9, 20.9, 22.7, 25.1, 25.4, 26.8, 27.8, 27.9, 28.1, 29.3, 29.4, 29.6, 30.9, 31.3, 31.8, 31.9, 32.1, 32.3, 34.4, 35.7, 48.6, 50.0, 50.8, 62.9, 63.1, 64.7, 71.3, 77.3, 79.4, 94.7, 98.3, 101.4, 125.8, 126.0, 128.3, 128.5, 141.6, 142.2, 176.5, 178.3, 180.1; MS (FAB), *m/z* (%) 419 (16) [M+1], 335 (78), 317 (100), 299 (30), 271 (16).

5.3.4. (2*S*)-2-[(1*R*)-1-(Tetrahydropyran-2-yloxy)octyl]-dodecanoic acid (18ca). Eluents for flash chromatography: 10 and 20% ethyl acetate in petroleum ether, yield: 85%. TLC (petroleum ether/ethyl acetate, 8:2): R_f=0.53; IR (neat): 3400–2500 (br), 1707 (s) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ (both diastereomers)=0.84–0.89 (m, 6H, 2×CH_3), 1.18–1.4 (m, 26H, $(CH_2)_8$, $(CH_2)_5$), 1.4–1.95 (m, 10H, 2×CH_2, $(CH_2)_3$(THP)), 2.41–2.52, 2.60–2.70, 2.73–2.82 (m, 1H, CHC(O)), 3.44–3.58, 3.70–3.78, 3.79–3.91, 3.92–4.05 (m, 3H, CH_2O, CHOTHP), 4.58–4.62, 4.71–4.77, 4.91–4.96 (m, 1H, CH(THP)); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ (both diastereomers)=14.1, 19.7, 20.7, 22.7, 25.1, 25.5, 25.7, 26.0, 26.7, 27.7, 27.8, 28.0, 29.2, 29.3, 29.5, 29.6, 30.7, 31.2, 31.8, 31.9, 32.1, 34.1, 48.3, 50.0, 50.8, 62.8, 62.9, 64.4, 72.1, 79.9, 94.7, 97.9, 100.9, 176.3, 178.6, 180.0; MS (FAB), *m/z* (%) 413 (8) [M+1], 329 (42), 311 (100), 293 (28).

5.4. Preparation of the Wang ester 19aa, 19ba, 19cb, 19ca

Wang resin (154 mg, 0.2 mmol) was suspended in dry CH_2Cl_2 and left to swell for 30 min followed by filtration. To a solution of acid **18** (0.6 mmol) and MeIm (0.142 ml, 1.8 mmol) in dry CH_2Cl_2 (3 ml) was added MSNT (178 mg, 0.6 mmol) at room temperature. The reaction solution was immediately added to the resin, and the resulting mixture agitated at room temperature for 12 h. Then Ac_2O (0.09 ml, 0.9 mmol) and pyridine (0.07 ml, 0.9 mmol) were added, and the mixture was agitated for 1 h to block any unreacted hydroxyl groups on the resin. The resulting resin was filtered, washed successively with CH_2Cl_2 (2×), [MeOH (2×), DMF (2×)]×2, CH_2Cl_2 (3×) and Et_2O (2×) and dried in vacuo. Each wash was carried out using 2 ml solvent and agitating the resin suspension for 2 min.

5.5. Removal of the THP protecting group to give the hydroxy esters 20aa, 20ba, 20cb, 20ca

After swelling of loaded resin **19** in CH_2Cl_2 for 30 min and subsequent filtration, the resin was suspended in CH_2Cl_2/MeOH 1:1 (2 ml) (containing dioxane (0.06 ml)) and treated with *p*TsOH (10 mg) for 7 h at room temperature. After filtration, the resulting resin **20** was washed with CH_2Cl_2 (3×), [MeOH, CH_2Cl_2]×2, CH_2Cl_2 (2×) and Et_2O (2×) and dried in vacuo. To monitor the deprotection progress, aliquots (20 μl) of the deprotection solution were removed in intervals of 1 h and diluted with CH_2Cl_2 (80 μl). A sample of this solution (0.5 μl) was then injected into a GC capillary column (30 m×0.32 mm×1 μm) at 50°C. GC was then performed using the following temperature program: 2 min 50°C, increase (rate 5°C/min) to 70°C, 1 min 70°C. Deprotection was judged complete when the ratio of the peak areas of methoxytetrahydropyran (t_R=5.8 min) and dioxane (as an internal standard, t_R=2.8 min) was constant.

5.6. Coupling of the Fmoc protected γ-amino acid 11 with the hydroxy esters 20

Loaded resin **20** (0.2 mmol) was washed with dry CH_2Cl_2 (2×3 ml) and then left in dry CH_2Cl_2 (3 ml) to swell for 30 min followed by filtration. To a solution of amino acid **11** (0.29 g, 0.6 mmol) and MeIm (0.142 ml, 1.8 mmol) in dry CH_2Cl_2 (3 ml) was added MSNT (0.178 g, 0.6 mmol) at room temperature. The reaction solution was added immediately to the resin, and the resulting mixture was shaken for 12 h at room temperature. After removal of the reactants by filtration, the resulting resin **21** was washed and dried as described in the procedure for esterification of the resin OH groups. The filtrates of the reaction mixture and of the CH_2Cl_2 washings were combined, washed with aqueous HCl (1N) and water, dried ($MgSO_4$) and evaporated in

vacuo to give crude starting material **11**. After purification of the residue by flash chromatography (20 and 10% petroleum ether in ethyl acetate), 50% of Fmoc protected γ-amino acid **11** could be recovered. To determine the coupling yield, a weighed sample of the dry resin **21** (~1 mg) was treated with 20% piperidine in DMF (0.5 ml) for 5 min to release the Fmoc group. After accurate dilution with DMF to 5 ml, the UV absorption of the solution based on the formed dibenzofulvene-piperidine adduct was measured at λ=301 nm (ϵ_{301}=7800) and 289 nm (ϵ_{289}=5800). The loading x (mmol Fmoc/g resin) was then obtained from the equation: $x=E_\lambda V/\epsilon_\lambda dy$ with V=5 ml, d=1 cm, y=weight of the resin sample in g. Coupling yields are listed in Table 1.

5.7. Cleavage of the Fmoc protecting group from 21aa, 21ba, 21cb, 21ca to give the diesters 22aa, 22ba, 22cb, 22ca

Loaded resin **21** was suspended in DMF (3 ml) and allowed to swell for 5 min. After removal of DMF by filtration, it was treated with 20% piperidine in DMF (2 ml) for 5 min at room temperature, then filtered, washed with DMF (2 ml) and treated again with 20% piperidine in DMF (2 ml) for 2 min. Longer cleavage times are critical because of hydrolysis of the ester bond. After removal of the cleavage solution by filtration, the resulting resin **22** was washed with [DMF (2×), MeOH (2×)]×2, CH_2Cl_2 (4×) and Et_2O (2×) and dried in vacuo.

5.8. Coupling of the Fmoc protected amino acids 23a–c with the amino esters 22

Loaded resin **22** was washed with dry CH_2Cl_2 (2×3 ml), then allowed to swell in dry CH_2Cl_2 (3 ml) for 30 min, and finally filtered. To a mixture of Fmoc protected amino acid **23** (3 equiv.) and PyBroP (3 equiv.) in dry CH_2Cl_2 (3 ml) was added DIEA (6 equiv.) at room temperature. The reaction solution was added immediately to the resin, and the resulting mixture was shaken at room temperature for 12 h. After removal of the reactants by filtration, the resulting resin **24** was washed with [DMF (2×), MeOH (2×)]×2, CH_2Cl_2 (4×) and Et_2O (2×) and dried in vacuo. The coupling yield was estimated analogous to the procedure described above for loaded resin **21**. The results are listed in Table 1.

5.9. Cleavage of the Fmoc protected amino acids 25 from the resin

After swelling of the loaded resin **24** in CH_2Cl_2 (3 ml) for 10 min and subsequent filtration, CH_2Cl_2/TFA 1:1 (2 ml) was added to the resin, and the mixture agitated at room temperature for 1 h resulting in a color change to dark violet. After filtration and washing of the resin with CH_2Cl_2 (4×3 ml), all filtrates were combined, diluted with CH_2Cl_2 (10 ml), washed with water (2×10 ml) to remove TFA, dried (Na_2SO_4) and concentrated in vacuo. Purification of the residue by flash chromatography gave the Fmoc protected amino acids **25**. Yields of the isolated products are listed in Table 1.

5.10. Deprotection of the amino group and macrocyclization of the amino acids 5 to the hapalosin analogs 4

To a solution of Fmoc protected amino acid **25** (for scale see Table 1) in THF (1.5 ml) was added diethylamine (0.5 ml) at 0°C. The mixture was stirred at 0°C for 10 min, then at room temperature for 2 h and then concentrated in vacuo. The residue was dissolved in DMF (1 l/mmol **25**) and the stirred solution was treated successively with TBTU (3 equiv.), HOBt (3 equiv.) and DIEA (4 equiv.) at room temperature. The resulting solution was stirred for 14 h and then partitioned between ethyl acetate and water. After separation of the layers and extraction of the water layer with ethyl acetate (2×), the organic layers were combined, washed successively with water, 5% aqueous $KHSO_4$, water, half-saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. The pure macrocycles **4** were obtained by flash chromatography.

5.10.1. (2*R*,3*S*,6*S*,9*S*,10*R*)-9-Benzyl-2-heptyl-10-hydroxy-6-isopropyl-3,8-dimethyl-1-oxa-5,8-diazacyclododecane-4,7,12-trione (4aaa). Eluents for flash chromatography: 50 and 40% petroleum ether in ethyl acetate, yield: 0.006 g (60%, based on **25aaa**). $[\alpha]^{24}_D$=−21.2 (*c* 0.404, CH_2Cl_2); TLC (petroleum ether/ethyl acetate, 1:1): R_f=0.27; ^{1}H NMR (250 MHz, $CDCl_3$): δ=0.04 (d, *J*=6.5 Hz, 3H, CH_3(*i*Pr)), 0.53 (d, *J*=6.8 Hz, 3H, CH_3(*i*Pr)), 0.81–0.86 (m, 3H, CH_3), 1.09 (d, *J*=7.1 Hz, 3H, CH_3), 1.14–1.38 (m, 10H, $(CH_2)_5$), 1.60–1.76 (m, 2H, CH(*i*Pr), CH_2), 2.08–2.26 (m, 1H, CH_2), 2.49–2.68 (m, 2H, CH_2Ph, CH_2C(O)), 2.80 (s, 3H, NCH_3), 2.86 (dd, *J*=5.2, 17.9 Hz, 1H, CH_2C(O)), 3.03–3.08 (m, 1H, CHC(O)), 3.41 (dd, *J*=2.2, 13.9 Hz, 1H, CH_2Ph), 3.58 (dd, *J*=9.4, 9.4 Hz, 1H, CH*i*Pr), 3.74–3.82 (m, 1H, C*H*OH), 3.83–3.93 (m, 1H, CHN), 4.76–4.84 (m, 1H, CHOC(O)), 6.24 (d, *J*=10.4 Hz, 1H, NH), 7.08–7.32 (m, 5H, aryl H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=13.0, 14.1, 17.7, 19.0, 22.6, 26.6, 27.9, 28.3, 29.1, 29.2, 29.9, 31.8, 36.0, 37.1, 41.7, 54.1, 60.7, 70.2, 78.8, 126.9, 128.8, 130.0, 137.6, 170.2, 171.7, 171.8; HRMS (EI): calcd for $C_{28}H_{44}N_2O_5$ 488.32499, found 488.32773.

5.10.2. (2*R*,3*S*,6*S*,9*S*,10*R*)-9-Benzyl-2-heptyl-10-hydroxy-3,6,8-trimethyl-1-oxa-5,8-diazacyclododecane-4,7,12-trione (4aab). Eluent for flash chromatography: 20% petroleum ether in ethyl acetate, yield: 0.021 g (33%, based on **25aab**). $[\alpha]^{24}_D$=−14.0 (*c* 0.436, CH_2Cl_2); TLC (petroleum ether/ethyl acetate, 2:8): R_f=0.42; ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.65 (d, *J*=6.6 Hz, 3H, CH_3 (6-Me)), 0.88 (m, 3H, CH_3), 1.07 (d, *J*=7.1 Hz, 3H, CH_3 (3-Me)), 1.15–1.73 (m, 10H, $(CH_2)_5$), 1.61–1.73, 2.04–2.15 (m, 2H, CH_2), 2.56 (dd, *J*=1.4, 15.9 Hz, 1H, CH_2C(O)), 2.65 (dd, *J*=10.7, 13.7 Hz, 1H, CH_2Ph), 2.86 (s, 3H, NCH_3), 2.83–2.92 (m, 1H, CH_2C(O)), 2.99 (dq, *J*=6.7, 7.1 Hz, 1H, CHC(O)), 3.36 (dd, *J*=1.8, 13.7 Hz, 1H, CH_2Ph), 3.72–3.88 (m, 3H, CHMe, CHN, C*H*OH), 4.74–4.81 (m, 1H, CHOC(O)), 6.16 (d, *J*=9.7 Hz, 1H, NH), 7.13–7.27, 7.27–7.36 (m, 5H, aryl H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=12.6, 14.1, 17.2, 22.6, 26.5, 27.8, 28.6, 29.2, 31.7, 35.5, 37.9, 41.5, 44.4, 61.3, 70.1, 78.9, 126.9, 128.7, 129.6, 137.5, 170.4, 170.9, 172.6; HRMS (EI): calcd for $C_{26}H_{40}N_2O_5$ 460.29369, found 460.29928.

5.10.3. (2*R*,3*S*,6*S*,9*S*,10*R*)-6,9-Dibenzyl-2-heptyl-10-hydroxy-3,8-dimethyl-1-oxa-5,8-diazacyclododecane-4,7,12-trione (4aac). Eluents for flash chromatography: 50 and 40% petroleum ether in ethyl acetate, yield: 0.043 g (44%, based on **25aac**). $[\alpha]^{25}_{D}=-6.0$ (*c* 0.764, CH_2Cl_2); TLC (petroleum ether/ethyl acetate, 1:1): $R_f=0.29$; ^1H NMR (400 MHz, $CDCl_3$): $\delta=0.76$ (d, $J=7.2$ Hz, 3H, CH_3 (3-Me)), 0.85 (t, $J=6.7$ Hz, 3H, CH_3), 1.10–1.33 (m, 10H, $(CH_2)_5$), 1.52–1.61, 1.96–2.07 (m, 2H, CH_2), 2.29 (dd, $J=4.9$, 13.9 Hz, 1H, CH_2Ph(6-Bn)), 2.52–2.70 (m, 3H, $CH_2C(O)$, CH_2Ph(6-Bn), CH_2Ph(9-Bn)), 2.84–2.94 (m, 2H, $CH_2C(O)$, CHC(O)), 2.89 (s, 3H, NCH_3), 3.37 (dd, $J=1.4$, 13.3 Hz, 1H, CH_2Ph(9-Bn)), 3.81–3.86 (m, 2H, C*H*OH, CHN), 3.90–3.97 (m, 1H, CHBn), 4.65–4.73 (m, 1H, CHOC(O)), 6.24 (d, $J=10.3$ Hz, 1H, NH), 6.77–6.83 (m, 2H, aryl H), 7.05–7.41 (m, 8H, aryl H); ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta=12.4$, 14.0, 22.6, 26.5, 27.8, 28.7, 29.1, 29.2, 31.7, 35.3, 37.6, 37.7, 41.3, 49.5, 60.7, 70.1, 79.0, 126.2, 127.0, 127.7, 128.4, 128.8, 129.5, 129.8, 129.9, 137.0, 137.7, 170.5, 170.9, 172.0; HRMS (EI): calcd for $C_{32}H_{44}N_2O_5$ 536.32502, found 536.33003.

5.10.4. (2*R*,3*S*,6*S*,9*S*,10*R*)-3,9-Dibenzyl-2-heptyl-10-hydroxy-6-isopropyl-8-methyl-1-oxa-5,8-diazacyclododecane-4,7,12-trione (4baa). Eluents for flash chromatography: 50 and 40% petroleum ether in ethyl acetate, yield: 0.013 g (64%, based on **25baa**). $[\alpha]^{24}_{D}=-35.3$ (*c* 0.23, CH_2Cl_2); TLC (petroleum ether/ethyl acetate, 1:1): $R_f=0.29$; ^1H NMR (400 MHz, $CDCl_3$): $\delta=-0.04$ (d, $J=6.7$ Hz, 3H, CH_3(*i*Pr)), 0.10 (d, $J=6.7$ Hz, 3H, CH_3(*i*Pr)), 0.91 (m, 3H, CH_3), 1.28–1.53 (m, 11H, $(CH_2)_5$, CH(*i*Pr)), 1.80–1.90 (m, 1H, CH_2), 2.31–2.43 (m, 1H, CH_2), 2.54 (dd, $J=1.3$, 17.9 Hz, 1H, $CH_2C(O)$), 2.64 (dd, $J=10.7$, 13.9 Hz, 1H, CH_2Ph(9-Bn)), 2.71 (dd, $J=4.1$, 13.0 Hz, 1H, CH_2Ph(3-Bn)), 2.81 (s, 3H, NCH_3), 2.92 (dd, $J=4.9$, 17.9 Hz, 1H, $CH_2C(O)$), 2.01 (dd, $J=11.2$, 13.0 Hz, 1H, CH_2Ph(3-Bn)), 3.38 (ddd, $J=4.1$, 6.8, 11.2 Hz, 1H, CHC(O)), 3.46 (dd, $J=1.8$, 13.9 Hz, 1H, CH_2Ph(9-Bn)), 3.59 (dd, $J=7.6$, 10.3 Hz, 1H, CH*i*Pr), 3.78–3.91 (m, 2H, CHN, C*H*OH), 4.81–4.95 (m, 1H, CHOC(O)), 5.84 (d, $J=10.3$ Hz, 1H, NH), 7.15–7.35 (m, 10H, aryl H); ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta=14.1$, 17.1, 19.0, 22.7, 26.7, 28.2, 28.3, 29.2, 29.7, 31.8, 34.4, 35.8, 36.9, 50.1, 54.1, 60.7, 70.1, 78.5, 126.8, 126.9, 128.6, 128.8, 129.9, 137.6, 138.1, 170.3, 171.7; HRMS (EI): calcd for $C_{34}H_{48}N_2O_5$ 564.35628, found 564.35795.

5.10.5. (2*R*,3*S*,6*S*,9*S*,10*R*)-9-Benzyl-3-decyl-10-hydroxy-6-isopropyl-8-methyl-2-(2-phenylethyl)-1-oxa-5,8-diazacyclododecane-4,7,12-trione (4cba). Eluent for flash chromatography: 50% petroleum ether in ethyl acetate, yield: 0.008 mg (43%, based on **25cba**). $[\alpha]^{25}_{D}=0$ (*c* 0.16, CH_2Cl_2); TLC (petroleum ether/ethyl acetate, 1:1): $R_f=0.26$; ^1H NMR (400 MHz, $CDCl_3$): $\delta=0.10$ (d, $J=6.8$ Hz, 3H, CH_3(*i*Pr)), 0.61 (d, $J=6.8$ Hz, 3H, CH_3(*i*Pr)), 0.86 (m, 3H, CH_3), 1.10–1.35 (m, 16H, $(CH_2)_8$), 1.64–1.76 (m, 3H, CH_2, CH(*i*Pr)), 1.98–2.08 (m, 1H, CH_2Bn), 2.47–2.71 (m, 4H, CH_2Ph, $CH_2C(O)$, CH_2Bn, CH_2Ph(9-Bn)), 2.83 (s, 3H, NCH_3), 2.79–2.86 (m, 1H, CH_2Ph), 2.87–2.97 (m, 2H, $CH_2C(O)$, CHC(O)), 3.46 (dd, $J=1.8$, 13.9 Hz, 1H, CH_2Ph(9-Bn)), 3.71 (dd, $J=8.0$, 10.4 Hz, 1H, CH*i*Pr), 3.81–3.87 (m, 1H, C*H*OH), 3.88–3.96 (m, 1H, CHN), 4.73–4.81 (m, 1H, CHOC(O)), 6.06 (d, $J=10.4$ Hz, 1H, NH), 7.10–7.35 (m, 10H, aryl H); ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta=14.1$, 17.9, 19.1, 22.7, 28.1, 28.3, 29.3, 29.4, 29.5, 30.1, 31.9, 32.5, 36.0, 37.1, 48.3, 54.3, 60.7, 70.1, 126.3, 127.0, 128.4, 128.7, 128.9, 130.0, 137.6, 140.3, 169.9, 171.3, 171.7; HRMS (EI): calcd for $C_{38}H_{56}N_2O_5$ 620.41888, found 620.42180.

5.10.6. (2*R*,3*S*,6*S*,9*S*,10*R*)-9-Benzyl-3-decyl-2-heptyl-10-hydroxy-6-isopropyl-8-methyl-1-oxa-5,8-diazacyclododecane-4,7,12-trione (4caa). Eluents for flash chromatography: 30 and 40% ethyl acetate in petroleum ether, yield: 0.035 g (57%, based on **25caa**). $[\alpha]^{25}_{D}=-4.2$ (*c* 0.717, CH_2Cl_2); TLC (petroleum ether/ethyl acetate, 6:4): $R_f=0.32$; ^1H NMR (400 MHz, $CDCl_3$): $\delta=0.07$ (d, $J=6.6$ Hz, 3H, CH_3(*i*Pr)), 0.59 (d, $J=7.1$ Hz, 3H, CH_3(*i*Pr)), 0.85 (m, 6H, 2×CH_3), 1.08–1.41 (m, 27H, $(CH_2)_5$, $(CH_2)_8$, CH_2(decyl)), 1.68–1.77 (m, 3H, CH(*i*Pr), CH_2(decyl), CH_2(heptyl)), 2.18–2.30 (m, 1H, CH_2(heptyl)), 2.52–2.71 (m, 2H, $CH_2C(O)$, CH_2Ph), 2.83 (s, 3H, NCH_3), 2.88 (dd, $J=5.3$, 18.1 Hz, 1H, $CH_2C(O)$), 2.96–3.03 (m, 1H, CHC(O)), 3.44 (dd, $J=1.8$, 13.7 Hz, 1H, CH_2Ph), 3.68 (dd, $J=9.3$, 9.3 Hz, 1H, CH*i*Pr), 3.76–3.82 (m, 1H, C*H*OH), 3.86–3.94 (m, 1H, CHN), 4.76–4.83 (m, 1H, CHOC(O)), 6.64 (d, $J=10.2$ Hz, 1H, NH), 7.16–7.25, 7.26–7.33 (m, 5H, aryl H); ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta=14.1$, 17.9, 19.1, 22.7, 26.7, 28.0, 28.1, 28.2, 28.3, 29.2, 29.3, 29.4, 29.6, 30.1, 31.8, 31.9, 35.7, 37.0, 48.1, 54.4, 60.6, 70.1, 78.7, 126.9, 128.8, 130.0, 137.6, 170.2, 171.5, 171.9; HRMS (EI): calcd for $C_{37}H_{62}N_2O_5$ 614.46583, found 614.46757.

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