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Total Synthesis and Configurational Assignment of the Marine Natural Product Haliclamide

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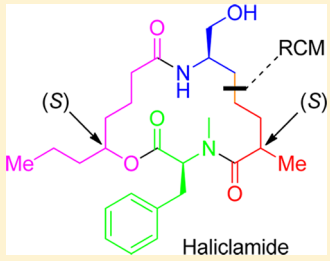
Supporting Information

ABSTRACT: The marine natural product haliclamide has been synthesized based on macrocyclization by ring-closing olefin metathesis. Using either enantiomer of two of the four building blocks that were employed to assemble the diene precursor for the metathesis reaction, three non-natural isomers of haliclamide were also prepared. On the basis of the comparison of the ^{1}H and ^{13}C NMR spectra of the individual stereoisomers with literature data for the natural product, the configuration of the previously unassigned stereocenters at C9 and C20 of haliclamide could be determined to be *S* for both carbons. The absolute configuration of haliclamide thus is 2*S*, 9*S*, 14*R*, 20*S*. The antiproliferative activity of synthetic haliclamide against several human cancer cell lines was found to be in the high μM range. The compound showed no antifungal or antibiotic activity.



INTRODUCTION

Marine organisms are a highly prolific source of biologically active secondary metabolites, many of which are potential lead structures for drug discovery in different areas.[1] At the same time, the amount of material available from natural sources is often insufficient for in-depth biological profiling; thus, the total synthesis of marine natural products is of crucial importance not only as a test ground for the assessment of the utility and practicality of synthetic methods, but also as an enabling means for natural product-based drug discovery and chemical biology.

Haliclamide (**1**; Figure 1) is a 16-membered cyclic depsipeptide which was isolated from the marine sponge *Haliclona sp*. by Randazzo et al.[2] and reported to exhibit *in vitro* antitumor activity against the human bronchopulmonary non-small cell lung carcinoma cell line NSCLC-N6 (IC_{50} = 4 μg/mL (8.7 μM)). Structurally, haliclamide (**1**) is composed of three different hydroxy or amino acid units, including *N*-methyl-L-phenylalanine (*N*-Me-L-Phe), 5-hydroxy octanoic acid (HOA), and 6-amino-7-hydroxy-2-methylheptanoic acid (AHMA). The two latter have not been found in any other natural product so far.

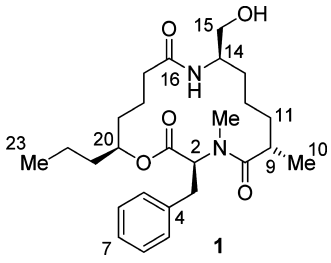


Figure 1. Structure of haliclamide (**1**). The configuration at C9 and C20 was only elucidated in the course of this work. Atom numbering is according to Randazzo et al.[2]

Given its considerable bioactivity and in light of its structural similarity with other depsipeptides of even higher potency, such as, for example, the actin assembly inhibitors doliculide,[3,4] jasplakinolide,[5−7] and chondramide C,[8,9] we felt that haliclamide (**1**) should be an interesting and relevant target for total synthesis and SAR studies.[10] Unfortunately, however, the stereochemistry of haliclamide (**1**) had not been fully resolved by Randazzo et al. in their original structural work.[2] While the configuration at C2 and C14 was firmly established as *S* and *R*, respectively, the configuration of the stereocenters at C9 and C20 remained unassigned. No attempts have been reported subsequent to the original isolation work to determine the configuration of these stereocenters, either through total synthesis or by other means.

In this paper we now report the ring-closing metathesis (RCM)-based stereoselective synthesis of natural haliclamide and the concurrent elucidation of its absolute configuration as that of **1** (Figure 1) by spectral comparison with published data for the natural product. Three other isomers of haliclamide with a 2*S*,14*R* configuration (atom numbering according to Randazzo et al.; Figure 1) were also prepared as part of this work following the same strategy. Although not all of these compounds were ultimately obtained (or even attempted to be obtained) as pure stereoisomers, their availability allowed the

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Scheme 1. Retrosynthesis of Haliclamide (1)

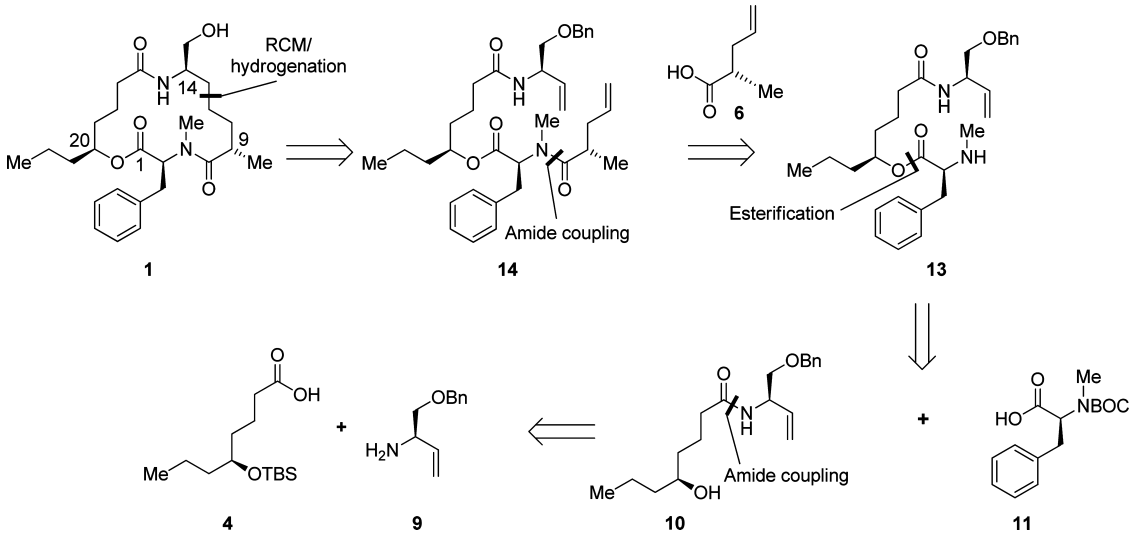
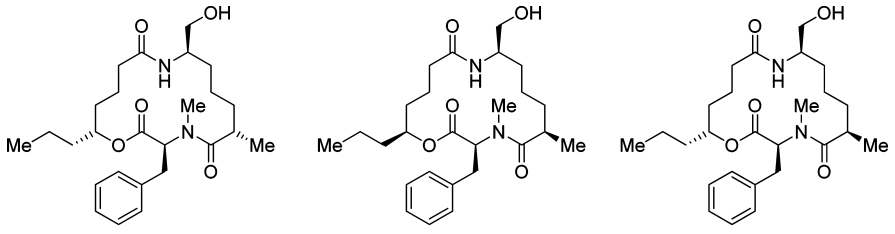


Chart 1



unambiguous identification of the diastereoisomer corresponding to natural haliclamide. The latter was prepared in 92% purity, with its 20*R* epimer as the only, but inseparable impurity. With **1** in hand, we have assessed its cytotoxicity against a broader range of human cancer cell lines than previously reported.

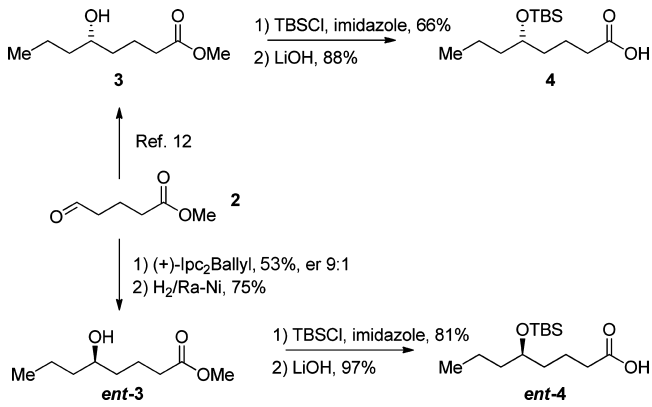
RESULTS AND DISCUSSION

As illustrated in Scheme 1 the retrosynthesis of diastereoisomer **1**, which was eventually shown to correspond with natural haliclamide, in the first major disconnection led to diene **14** as the substrate for macrocyclization through RCM.[11] This was to be followed by simultaneous reduction of the double bond and removal of the benzyl protecting group. Diene **14** would be obtained by amide coupling of acid **6** with secondary amine **13**; the latter could be disconnected further into alcohol **10** and *N*-Boc protected *N*-Me-L-Phe (**11**). Intermediate **10** was envisaged to result from condensation of acid **4** with amine **9**, which in turn was to be derived from L-serine as the source of chirality at C14 (haliclamide numbering). Finally, the chiral center in acid **4** was to be established by asymmetric Brown allylation,[12] while acid **6** would be accessible through stereoselective allylation of (4*R*)-4-benzyl-3-propionyl-1,3-oxazolidin-2-one.[13,14]

The three other haliclamide isomers with a 2*S*,14*R* configuration, that is, **1-*SR*** (9*S*,20*R* configuration), **1-*RS*** (9*R*,20*S*), and **1-*RR*** (9*R*,20*R*) (Chart 1) were to be obtained in a completely analogous fashion, employing the enantiomers of building blocks **4** and **6**, that is, ***ent*-4** and ***ent*-6**, respectively.

Synthesis of Building Blocks. Carboxylic acid **4** was obtained from δ-valerolactone via known aldehyde **2**[15] and ester **3**[12] (er 93:7); silylation of **3** followed by ester saponification provided the desired acid **4** in 58% overall yield (Scheme 2).

Scheme 2. Synthesis of Carboxylic Acids 4 and *ent*-4



The enantiomeric acid ***ent*-4**, which has not been described in the literature previously, was obtained from **2** in complete analogy to **4**. Thus, Brown allylation of **2** with (+)-Ipc$_2$B-(CH$_2$CH=CH$_2$) at −100 °C and subsequent hydrogenation of the ensuing (crude) homoallylic alcohol with Ra−Ni gave ester ***ent*-3** in 39% yield (based on **2**) with an er of 9:1. Silylation and ester saponification then furnished ***ent*-4**.

Carboxylic acid **6** was prepared from oxazolidinone **5**[13] by hydrolytic removal of the auxiliary with LiOOH in 76% yield

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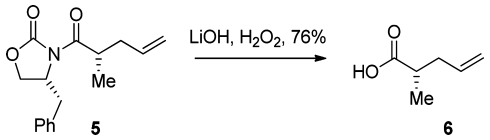
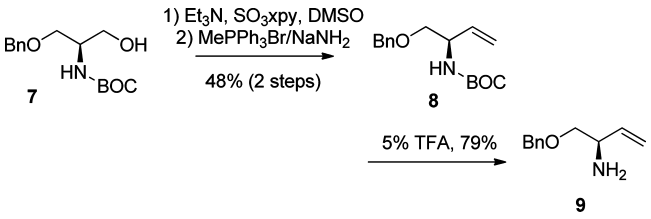
(Scheme 3). Likewise, saponification of *ent*-**5**[16] gave *ent*-**6** in a yield of 73% (not shown).

Scheme 3. Synthesis of Carboxylic Acid 6



The synthesis of olefin **9** proceeded through primary alcohol **7** (Scheme 4), which was obtained from commercially available

Scheme 4. Synthesis of Amine 9

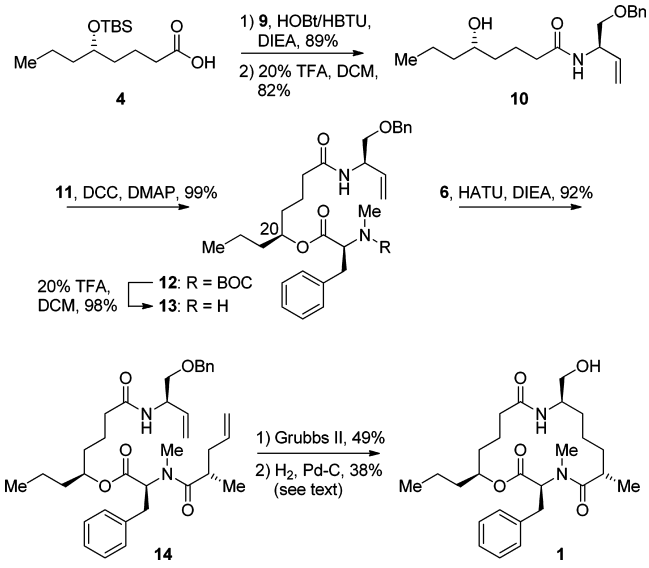


N-Boc-L-Ser(OBn)−OH by LAH reduction.[17] Subsequent oxidation with SO_3•pyridine complex followed by Wittig olefination of the crude aldehyde using Schlosser's "instant ylide"[18] then gave the corresponding olefin **8** in 48% overall yield (from **7**). Boc-cleavage with 5% TFA in DCM in the presence of triisopropylsilane (TIPS)[19] finally delivered the desired allylic amine **9** in 79% yield. The efficiency of the olefination step critically depended on the method employed for the oxidation of **7**, with the use of the crude aldehyde obtained through Swern oxidation resulting in significantly lower yields of olefination product. Initial attempts at preparing the intermediate aldehyde by DIBAL-H reduction of Boc-L-Ser(OBn)-OMe[20] only yielded the corresponding primary alcohol **7**.

As α-amino aldehydes generally undergo Wittig reactions with little epimerization,[21] we felt that the approach followed for the synthesis of **9** should have delivered the compound in good optical purity. On the other hand, the optical rotatory power of this intermediate was somewhat lower than literature values (+7.2° vs. +10.2°;[22] −11.3°[23] and −16.5°[24] for *ent*-**9**), which indicated that some erosion of stereochemical integrity might have occurred in the elaboration of *N*-Boc-L-Ser(OBn)−OH into olefin **9**; this supposition was in fact corroborated later.

Assembly of Building Blocks and Ring Closure. The elaboration of building blocks **4**, **6**, and **9** into diene **14** commenced with the O-benzotriazolyl-*N*,*N*,*N*′,*N*′-tetramethyl-uronium hexafluorophosphate (HBTU)[25]-mediated coupling of acid **4** with amine **9**, which gave the desired amide in excellent chemical yield (89%, Scheme 5). Removal of the TBS group from the coupling product with 20% TFA in DCM proceeded smoothly to furnish the free alcohol **10** in high yield. While routine analysis of the coupling product by ^{1}H NMR spectroscopy indicated the presence of a single compound (before as well as after TBS deprotection), careful inspection of the corresponding ^{13}C NMR spectra showed signal splitting for several carbon atoms for the immediate (TBS-protected) coupling product and **10**, respectively. At the same time, amide **10** appeared to be homogeneous by TLC. DCC/DMAP-mediated coupling of **10** with Boc-*N*-Me-L-Phe-OH (**11**)

Scheme 5. Building Block Assembly and Synthesis of 1



followed by Boc-removal with 20% TFA/DCM then gave the free amino ester **13** in excellent yield (97% for two steps). However, although homogeneous by TLC, ^{13}C NMR analysis showed **13** to be a mixture of at least two diastereoisomers; in contrast, no clear indication for the presence of diastereoisomers was evident from the corresponding ^{1}H NMR spectra, thus precluding even a rough determination of the isomer ratio by the integration of specific ^{1}H NMR signals.

As for intermediates **10**, **12**, and **13**, chromatographically (TLC, FC) inseparable mixtures were also observed for the corresponding intermediates derived from *ent*-**4** or/and *ent*-**6**, based on the presence of two sets of signals in their ^{13}C NMR spectra (for some carbons). However, while the presence of mixtures of isomers was clearly unsatisfactory, the materials obtained at this point were still processed further, assuming that the separation of diastereoisomers would be feasible by HPLC after macrocyclization. Thus, *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyl-uronium hexafluoro-phosphate (HATU)[26]-mediated coupling of acid **6** with amino ester **13** gave diene **14** as the substrate for the key cyclization step (Scheme 5). HATU was preferred over other coupling reagents in this step, as it has been shown to provide for optimal coupling efficiency in reactions involving secondary amino groups.[26] Subsequent RCM of **14** was accomplished with second generation Grubbs catalyst[27] in refluxing toluene, to provide a mixture of isomeric macrocycles in 49% total yield. Not unexpectedly at this stage, ^{1}H NMR analysis indicated the presence of at least 3 isomers (at least partly due to the (inconsequential) formation of double bond isomers in the RCM step) that were inseparable either by TLC or FC. The mixture of RCM-products (after filtration over silica gel) was then submitted to catalytic hydrogenation over Pd/C in MeOH, leading to simultaneous double bond reduction and cleavage of the benzyl ether moiety. Purification of the hydrogenation products by FC gave 38% of an inseparable (by FC) 92:8 mixture of two isomers (based on ^{1}H NMR; isomer I and isomer II, respectively) and 32% of a ca. 2:3 mixture of the I/II mixture and a third isomer III (based on reversed-phase (RP)-HPLC analysis; isomers I and II were inseparable also by HPLC).[28] Isomer I was eventually shown to be haliclamide (**1**) (*vide infra*).

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Isomers **1-*SR*** (9*S*, 20*R* configuration), **1-*RS*** (9*R*, 20*S*), and **1-*RR*** (9*R*, 20*R*) (Chart 1) were obtained from **13** (**1-*RS***) and 20*R*-**13** (haliclamide numbering; Figure 1) (**1-*SR*** and **1-*RR***) in full analogy to the preparation of **1** from **13**. As for the synthesis of **1**, mixtures of stereoisomers were obtained after the final hydrogenation step that could not be simply accounted for by the incomplete stereochemical purity of the starting building blocks **4**/***ent*-4**. While samples of isomers **1-*RS*** and **1-*SR*** with >90% purity could be isolated after FC, **1-*RR*** was obtained as a 3/1 mixture with its putative 14*S*-isomer (*vide infra*); however, the spectral data collected for these materials still allowed the unambiguous assignment of the C19 and C20 stereocenters in haliclamide. Thus, the ^{1}H and ^{13}C NMR spectra of the major isomer I that was derived from starting acids **4** and **6** matched perfectly with the spectral data published for the natural product by Randazzo et al. (Table 1).[2] In contrast, clear deviations from the published NMR data were apparent for isomers II and III (best visible in the ^{13}C NMR spectra, see Supporting Information); likewise, the NMR data collected for either **1-*SR***, **1-*RS***, or **1-*RR*** were clearly different from those published for haliclamide (Table 2). On the basis of these findings, the absolute configuration of haliclamide could be deduced as 2*S*,9*S*,14*R*,20*S* (corresponding to structure **1** in Figure 1). Isomer II was eventually shown to be **1-*SR***, with the 92/8 ratio of **1**/**1-*SR*** in the final product reflecting the imperfect optical purity of acid **4** (*S*/*R* ratio of ca. 93/7).

While the presence of isomer II could be readily traced to the er for acid **4**, the detection of substantial amounts of a third haliclamide isomer in the final mixture of hydrogenation products in the synthesis of **1** (and also the isolation of major isomeric impurities in the syntheses of **1-*SR***, **1-*RS***, and **1-*RR***) was somewhat puzzling. However, as briefly discussed above, the optical rotatory power of amine **9** had indicated that this building block might not to be a single enantiomer, which would have been a plausible cause for the formation of (additional) diastereomeric products after its coupling with acid **4** and at all subsequent stages of the synthesis. In order to clarify this issue, the optical purity of **9** was analyzed in a more rigorous way, based on its derivatization with Marfey's reagent (1-fluoro-2,4-dinitrophenyl-5-L-alaninamide (FDAA)).[29,30] HPLC-MS analysis of the resulting product mixture revealed two peaks with the expected mass for the FDAA derivative of **9** in a ratio of ca. 5/1 (ΔR_t ca. 0.8 min; see Supporting Information). Comparison with the FDAA derivative of *ent*-**9** (prepared from Boc-D-Ser(OBn)−OH according to Scheme 4) clearly established the two peaks to be the FDAA derivatives of *R*- and *S*-**9**, respectively. While these numbers do not fully match with the ratio of isomers I and III in the final product mixture (which was ca. 5/2), the data strongly suggest that the difference between these isomers was indeed the configuration at C14;[31] isomer III was thus tentatively assigned as the 14*S* analog of natural haliclamide.[32] By inference, the major isomeric side products obtained in the syntheses of **1-*SR***, **1-*RS***, and **1-*RR*** are assumed to be the respective 14*S* epimers; independent of this assumption, it is clear that none of these compounds corresponds to natural haliclamide. Interestingly, the ratio of 14*R*/14*S* isomers for the total amount of material isolated after FC in all three cases proved to be lower than the 5/1 *R*/*S* ratio in the starting building block **9** (**1-*SR***: 14*R*/14*S* = 1.44, for a total combined yield of 21% for the cyclization and hydrogenation steps; **1-*RS***: 1.39, 48%; **1-*RR***: 1.95, 50%). The reasons for this apparent discrepancy are unclear at this point; a detailed investigation of this finding, however, was outside of the scope of the current study.

Table 1. NMR Spectroscopic Data for Synthetic 1 and Natural Haliclamide ($CDCl_3$, 500 MHz)[a]

	1		haliclamide	
atom number[b]	δ_C [ppm]	δ_H [ppm] (*J* in Hz)	δ_C [ppm]	δ_H [ppm] (*J* in Hz)
1	170.7		170.7	
2	56.3	5.90, dd (11.9, 5.3)	56.2	5.90, dd (12.4, 5.6)
3	34.2	2.95, dd (15.1, 12.0)	34.1	2.94, dd (14.6, 12.4)
		3.51, dd (14.7, 4.7)		3.51, dd (14.6, 5.6)
4	136.6		136.5	
5/5′	128.5	7.27, m	128.4	7.27, t (7.7)
6/6′	128.4	7.18, m	128.4	7.18, t (7.7)
7	126.8	7.20, m	126.7	7.20, t (7.7)
NMe	31.2	2.84, s	31.2	2.83, s
8	178.2		178.2	
9	36.4	2.65−2.57, m	36.4	2.60, m
10	18.0	0.65, d (7.0)	18.0	0.63, d (6.8)
11	31.4	1.74, m	31.3	1.72, m
		1.19, m		1.20, m
12	23.2	1.46, m	23.2	1.45, m
		1.07, m		1.02, m
13	27.8	2.15, m	27.7	2.14, m
		1.26, m		1.25, m
14	53.6	3.45−3.37, m	53.6	3.40, br m
15	65.7	3.73−3.66, m	65.7	3.68, br dd (11.6, 4.3)
		3.87, dd (12.1, 1.8)		3.87, d (11.6)
OH		5.16, br s		
NH		6.83, br d (5.7)		6.82, br d (5.6)
16	174.4		174.5	
17	36.4	2.47−2.40, m	36.6	2.43, m
		2.14, m		2.18, m
18	22.9	1.79, m	22.9	1.77, m
		1.61, m		1.60, m
19	32.0	1.62, m	31.9	1.62, m
		1.47, m		1.45, m
20	76.7	5.02−4.95, m	77.0	4.98, m
21	37.1	1.56, m	37.1	1.55, m
		1.48, m		1.50, m
22	18.5	1.46, m	18.5	
		1.32, m		1.32, m
23	14.0	0.93, t (7.3)	13.9	0.92, t (7.3)

[a]Data for natural haliclamide are from ref.[2] Data for synthetic **1** were obtained at 298 K; the measurement temperature for natural haliclamide is not indicated in ref 2. [b]For atom numbering see Figure 1.

With regard to the loss of optical purity during the elaboration of Boc-L-Ser(OBn)−OH into **9**, we speculated that partial racemization may have occurred at the stage of the aldehyde obtained from **7**, either during its formation/isolation or in the ensuing Wittig reaction.[33] In order to avoid this problem, we have developed an alternative synthesis of amine **9** that does not proceed through a potentially epimerization-prone α-amino aldehyde as an intermediate (Scheme 6).

The synthesis departed from acetonide **15**,[34,35] which was converted into mono-PMB-protected triol **16**[34,35] by cleavage with copper(II) chloride dihydrate[36] in 92% yield. Conversion of **16** into the corresponding cyclic dibutyltin acetal[37,38] followed by *in situ* benzylation gave the primary benzyl ether

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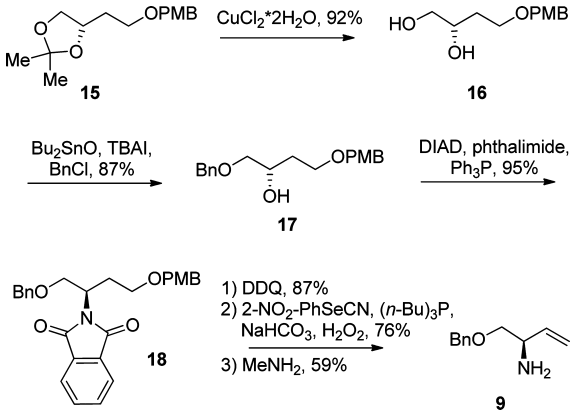
Table 2. Comparison of Characteristic ^{1}H-NMR Signals of Haliclamide (1), 1-*SR*, 1-*RS*, and 1-*RR*[a]

	haliclamide[b]	1	1-*SR*	1-*RS*	1-*RR*
atom number[c]	δ_H [ppm]	δ_H [ppm]	δ_H [ppm]	δ_H [ppm]	δ_H [ppm]
2	5.90, dd	5.90, dd	5.66, dd	3.69−3.64, m	3.65−3.58, m
NMe	2.83, s	2.84, s	2.93, s	2.68, s	2.62, s
10	0.63, d	0.65, d	0.81, d	1.05, d	0.90, d
20	4.98, m	5.02−4.92, m	4.95−4.89, m	5.06−5.00, m	4.90−4.82, m
23	0.92, t	0.93, t	0.83, t	0.93, t	0.82, t

[a]$CDCl_3$ at 500 MHz and 298K, except for 1-*RR* (400 MHz). [b]Data from ref 2; the measurement temperature is not indicated in ref 2. [c]For atom numbering see Figure 1.

Scheme 6. Alternative Synthesis of Amine 9



17 in excellent yield (87%);[39] subsequent Mitsunobu reaction with phthalimide as a nucleophile then furnished the N-substituted phthalimide 18 (95%).[24] DDQ-mediated cleavage of the PMB protecting group followed by Grieco-Sharpless olefination[40,41] and final phthalimide cleavage with methylamine[42] yielded the desired amine 9[22] in 39% yield for the three-step sequence from 18. (For syntheses of *ent*-9 see refs 23, 24). This material was elaborated into 1 through the same sequence of reactions as depicted in Scheme 5, with the chemical yields for the individual steps generally being comparable with those obtained in the synthesis with partially racemic 9. A notable exception is the final hydrogenation step, which provided a 92% yield of a 92/8 mixture of 1 and 1-*SR* (after FC) compared to a combined yield of 70% for the 92/8 mixture of 1/1-*SR* and the ca. 19/12/1 mixture of 14*S* haliclamide/1/1-*SR* that had been obtained previously. None of the (purported) 14*S* isomer of 1 was observed in this product and the analytical data of the material were identical with those of purified 1 derived from Boc-L-Ser(OBn)−OH (*vide supra*).[32] Unfortunately, we were not able to separate 1 and 1-*SR* either by FC or HPLC;[28] given the moderate biological activity of 1 (*vide infra*), no attempts were made to further improve the synthesis by elaborating more selective access to acid 4.

Synthetic haliclamide (1; 92% purity) was assessed for its antiproliferative activity against an array of human cancer cell lines, as only a single IC_{50} value had been reported for the natural material in the context of the isolation work (8.7 μM; against the NSCLC-N6 cell line).[2] The compound was found to inhibit human cancer cell growth *in vitro* with IC_{50} values between 26 and 52 μM after a 72 h exposure period and thus to be a moderately potent antiproliferative agent (Table 3). It remains to be investigated whether modified analogs of 1 with improved *in vitro* activity can be identified.

Table 3. Antiproliferative Activity of Haliclamide (1) against Human Cancer Cell Lines[a]

cell line	IC_{50} [μM]
A549 (lung)	26 ± 3.2
MCF-7 (breast)	31 ± 2.9
HCT-116 (colon)	28 ± 2.5
HL60 (leukemia)	52 ± 4.7
Jurkat (leukemia)	47 ± 3.2

[a]Cells were exposed to 1 for 72 h. Cell numbers were determined by an MTT assay. Numbers are average values of three experiments ± standard deviations.

EXPERIMENTAL SECTION

(*S*)-5-((*tert*-Butyldimethylsilyl)oxy)octanoic Acid (4). To a solution of ester 3[12] (4.63 g, 26.6 mmol) and imidazole (4.53 g, 66.5 mmol) in 50 mL of dry DCM was added TBSCl (6.03 g, 40 mmol) at 0 °C. The solution was allowed to warm to rt, stirred overnight and poured into a mixture of 300 mL Et_2O/300 mL of brine. The aq. phase was extracted twice with 250 mL Et_2O, the organic extracts were dried ($MgSO_4$) and the solvent evaporated. FC (hexane/EtOAc 4:1) gave 5.06 g of (*S*)-methyl 5-((*tert*-butyldimethylsilyl)-oxy)octanoate (66%) as a clear viscous liquid. $[\alpha]_D^{20}$ = +0.01° (*c* 0.60, $CHCl_3$).[43] ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.68−3.63 (m, 4H), 2.31 (*t*, *J* = 7.80 Hz, 2H), 1.75−1.57 (m, 2H), 1.49−1.25 (m, 6H), 0.90 (t, *J* = 7.31 Hz, 3H), 0.89 (s, 9H), 0.04 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.1, 71.7, 51.4, 39.3, 36.4, 34.3, 25.93, 25.90, 20.8, 18.5, 18.1, 14.3, −4.5. IR: ν 2978, 2955, 2860, 1742, 1462, 1361, 1252, 1142 cm^{-1}. HRMS (ESI) calcd for [$C_{15}H_{32}O_3Si$ + Na^+] 311.2013, found 311.2013.

A solution of (*S*)-methyl 5-((*tert*-butyldimethylsilyl)oxy)octanoate (5.79 g, 20 mmol) in 100 mL THF/water 4:1 and LiOH (2.49 g, 100 mmol) was stirred overnight at rt. The solvent was removed, 25 mL water added, and the pH adjusted to 4 with 1M HCl followed by extraction with DCM (2 × 200 mL). The organic extracts were dried ($MgSO_4$) and the solvent was evaporated to give 4 (4.86 g, 88%) as a clear viscous liquid. $[\alpha]_D^{20}$ = +0.01° (*c* 1.31, $CHCl_3$).[43] ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.75 (br s, 1H), 3.71−3.64 (m, 1H), 2.37 (t, *J* = 7.43 Hz, 2H), 1.76−1.26 (m, 8H), 0.91−0.87 (m, 12H), 0.04 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.4, 71.6, 39.3, 36.3, 34.1, 25.9, 20.5, 18.5, 18.1, 14.3, −4.45, −4.49. IR: ν 2956, 2860, 2360, 1708, 1254, 1140 cm^{-1}. HRMS (ESI) calcd for [$C_{14}H_{30}O_3Si$+Na^+] 297.1856, found 297.1855.

(*S*)-2-Methylpent-4-enoic Acid (6). To a solution of imide 5[13] (7.75 g, 29.2 mmol) in 90 mL THF/water 4:1 were added LiOH (2.79 g, 116.4 mmol) and 50% H_2O_2 (3.36 mL, 58.2 mmol). The mixture was stirred overnight at rt, the pH adjusted to 1−2 with 90 mL 1 M HCl, and the mixture extracted 3× with 300 mL Et_2O. The organic extracts were dried ($MgSO_4$), the solvent was evaporated and the residue distilled under reduced pressure (110 °C, 1 mbar) to give acid 6 (2.53 g, 76%) as a colorless liquid. $[\alpha]_D^{20}$ = +10.5° (*c* 1.92, $CHCl_3$) (lit.:[44] $[\alpha]_D^{22}$ = +10.1° (*c* 1.0, $CHCl_3$)). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.82−5.72 (m, 1H), 5.12−5.04 (m, 2H), 2.59−2.50 (m, 1H), 2.50−2.43 (m, 1H), 2.25−2.19 (m, 1H), 1.19 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR

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(100 MHz, $CDCl_3$): δ 182.2, 135.1, 117.2, 39.1, 37.4, 16.3. IR: ν 2979, 2666, 1703, 1643, 1417, 1244, 916 cm^{-1}. HRMS (ESI) calcd for $[C_6H_9O_2 + 2Na^+]$ 159.0392, found 159.0393.

(*R*)-*tert*-Butyl (1-(Benzyloxy)but-3-en-2-yl)carbamate (8). To a solution of alcohol **7**[17] (5.5 g, 19.5 mmol) and Et_3N (8.0 mL, 58.4 mmol) in 140 mL DCM was added a solution of SO_3•py-complex (9.3 g, 58.4 mmol) in 40 mL DMSO/30 mL DCM. After 30 min, 320 mL water were added at 0 °C and the mixture extracted 4x with 400 mL Et_2O. Each individual organic extract was washed twice with 100 mL 10% citric acid, 100 mL water, 100 mL sat. $NaHCO_3$, and again 100 mL water. The combined extracts were dried ($MgSO_4$) and the solvent was evaporated to give 4.85 g (89%) of crude aldehyde.

A suspension of $MePPh_3Br$/NaH (12.2 g, 29.2 mmol) in 170 mL THF was stirred for 1 h at 0 °C. A solution of the above crude aldehyde (4.85 g, 17.4 mmol) in 160 mL THF was then slowly added over a period of 1 h. After additional 2 h at 0 °C, 315 mL sat. NH_4Cl, 400 mL water, and 700 mL Et_2O were added at rt, the phases were separated and the aq. phase was extracted thrice with 600 mL Et_2O. The combined extracts were dried ($MgSO_4$) and the solvent evaporated. FC (hexane/EtOAc 5:1) gave 2.60 g of olefin **8** (48% over two steps) as a yellowish oil. $[\alpha]_D^{20}$ = +25.9° (*c* 1.40, $CHCl_3$) (lit.[45] (*ent*-**8**): $[\alpha]_D$ = −31.6° (*c* 1.0, CH_2Cl_2)). ^1H NMR (400 MHz, $CDCl_3$): δ 7.42−7.20 (m, 5H), 5.86 (ddd, *J* = 17.3, 10.4, 5.4 Hz, 1H), 5.32−5.10 (m, 2H), 4.90 (s, 1H), 4.63−4.45 (m, 2H), 4.32 (s, 1H), 3.53 (qd, *J* = 9.5, 4.6 Hz, 2H), 1.45 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 125.4, 138.0, 136.4, 128.4, 127.8, 127.7, 115.7, 80.0, 73.3, 72.1, 52.4, 28.4. IR: ν 3444, 3350, 3086, 3064, 3031, 2979, 2929, 2863, 2358, 1708, 1644, 1496, 1454, 1365, 1247, 1164, 1103, 1070, 1027, 991 cm^{-1}. MS (ESI): *m*/*z* (%) 178.0 $[M\text{-Boc} + 2H]^+$ (55), 222.1 $[M\text{-}t\text{-Bu} + 2H]^+$ (100), 278.3 $[M + H]^+$ (35), 300.2 $[M + Na]^+$ (10).

(*R*)-1-(Benzyloxy)but-3-en-2-amine (9). To a solution of **8** (1.2 g, 4.37 mmol) in 200 mL DCM were added triisopropylsilane (1.8 mL, 8.73 mmol) and 10 mL TFA and the mixture was stirred at rt for 2.5 h. It was then slowly poured into 400 mL sat. $NaHCO_3$ at 0 °C, 400 mL DCM were added, the phases were separated and the aq. solution extracted twice with 400 mL DCM. The combined extracts were dried ($MgSO_4$) and the solvent evaporated. FC (hexane/EtOAc 2:1 + 2% Et_3N) gave 607 mg of amine **9** (79%) as a dark yellow oil. $[\alpha]_D^{20}$ = +7.2° (*c* 1.35, $CHCl_3$) (lit.:[22] $[\alpha]_D^{24}$ = +10.2° (*c* 1.35, $CHCl_3$)). ^1H NMR (400 MHz, $CDCl_3$): δ 7.42−7.20 (m, 5H), 5.83 (dddd, *J* = 16.9, 10.4, 6.1, 1.5 Hz, 1H), 5.24 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.11 (dq, *J* = 10.4, 1.4 Hz, 1H), 4.54 (d, *J* = 1.7 Hz, 2H), 3.61 (dddd, *J* = 7.2, 5.1, 3.5, 1.8 Hz, 1H), 3.50 (ddd, *J* = 9.2, 4.1, 1.8 Hz, 1H), 3.31 (ddd, *J* = 9.4, 7.9, 1.7 Hz, 1H), 1.64 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.1, 138.2, 128.4, 127.7, 115.2, 75.0, 73.3, 53.9. IR: ν 3375, 3063, 3030, 2980, 2858, 2360, 2341, 1645, 1586, 1496, 1454, 1362, 1092, 1028, 993, 920, 736, 697 cm^{-1}. HRMS (ESI) calcd for $[C_{11}H_{15}NO + H^+]$ 178.1226, found 178.1227.

From Phthalimide 18. To a solution of **18** (1.03 g, 2.3 mmol) in 100 mL DCM/water 9:1 was added DDQ (630 mg, 2.8 mmol) at 0 °C. The mixture was stirred overnight at rt, diluted with DCM and washed with $NaHCO_3$. The organic phase was dried ($MgSO_4$) and the solvent evaporated. FC (hexane/EtOAc 1:1) furnished 657 mg (87%) of (*R*)-2-(1-(benzyloxy)-4-hydroxybutan-2-yl)isoindoline-1,3-dione. $[\alpha]_D^{25}$ = −0.75° (*c* 1.0, $CHCl_3$).[43] ^1H NMR (400 MHz, $CDCl_3$): δ 7.85−7.78 (m, 2H), 7.74−7.68 (m, 2H), 7.32−7.19 (m, 5H), 4.71 (dddd, *J* = 10.2, 9.0, 5.6, 4.7 Hz, 1H), 4.54 (d, *J* = 12.1 Hz, 1H), 4.48 (d, *J* = 12.1 Hz, 1H), 4.08 (dd, *J* = 9.9, 9.1 Hz, 1H), 3.76 (dd, *J* = 9.9, 5.8 Hz, 1H), 3.73−3.66 (m, 1H), 3.62−3.54 (m, 1H), 2.22−2.12 (m, 1H), 2.05−1.93 (m, 1H), 1.90 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.9, 137.9, 134.0, 131.9, 128.3, 127.6, 123.3, 72.9, 69.5, 59.4, 48.3, 31.9. IR: ν 3463, 2871, 1771, 1702, 1375, 1089, 1040, 882, 721, 699, 531 cm^{-1}. HRMS (ESI) calcd for $[C_{19}H_{19}NO_4 + H^+]$ 326.1387, found 326.1384.

To a solution of (*R*)-2-(1-(benzyloxy)-4-hydroxybutan-2-yl)-isoindoline-1,3-dione (1.23 g, 3.8 mmol) and 2-nitrophenyl selenocyanate (2.94 g, 12.9 mmol) in 30 mL THF was added (*n*-Bu)$_3$P (3.23 mL, 12.9 mmol) dropwise below 35 °C over a period of 15 min. The mixture was stirred for 1 h at rt, $NaHCO_3$ (9.9 g, 0.12 mol) and 30% H_2O_2 (13.2 mL, 0.12 mol) were added at *T* < 35 °C. The slurry was stirred for 24 h at rt, 120 mL of a 5% aq. $KHSO_4$ solution were added, the phases were separated, and the aqueous solution was extracted thrice with 100 mL Et_2O. The organic extracts were washed with water and brine and dried ($MgSO_4$). Solvent evaporation and FC (hexane/EtOAc 3:1) gave 950 mg (76%) of (*R*)-2-(1-(benzyloxy)but-3-en-2-yl)isoindoline-1,3-dione as a yellow oil. $[\alpha]_D^{20}$ = +4.69° (*c* 0.50, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.86−7.80 (m, 2H), 7.74−7.68 (m, 2H), 7.29−7.18 (m, 5H), 6.16 (ddd, *J* = 17.4, 10.3, 7.2 Hz, 1H), 5.31 (td, *J* = 17.2, 1.2 Hz, 1H), 5.25 (td, *J* = 10.4, 1.1 Hz, 1H), 5.13−5.03 (m, 1H), 4.56 (d, *J* = 12.1 Hz, 1H), 4.49 (d, *J* = 12.1 Hz, 1H), 4.11 (t, *J* = 9.9 Hz, 1H), 3.75 (dd, *J* = 10.0, 5.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.1, 137.9, 133.9, 132.3, 132.0, 128.3, 127.6, 123.2, 119.0, 72.8, 68.9, 53.2. IR: ν 2866, 2364, 2339, 1773, 1707, 1517, 1498, 1468, 1454, 1384, 1357, 1333, 1304, 1173, 1099, 1029, 993, 958, 936, 883, 869, 718, 699, 679, 672, 531 cm^{-1}. HRMS (ESI) calcd for $[C_{19}H_{17}NO_3+Na^+]$ 330.1101, found 330.1114.

A solution of (*R*)-2-(1-(benzyloxy)but-3-en-2-yl)isoindoline-1,3-dione (790 mg, 2.6 mmol) in 80 mL of 8 M $MeNH_2$ in EtOH was stirred for 2 h at rt. After solvent evaporation FC (hexane/EtOAc 2:1 + 2% Et_3N) gave 270 mg (59%) of amine **9** as a yellow oil. $[\alpha]_D^{24}$ = +10.2° (*c* 1.00, $CHCl_3$). NMR data of this material were identical with those of **9** derived from Boc-L-Ser(OBn)−OH.

(*S*)-*N*-((*R*)-1-(Benzyloxy)but-3-en-2-yl)-5-hydroxyoctanamide (10). To a solution of HBTU (1.95 g, 5.15 mmol) and 1-hydroxybenzotriazole (HOBt) (695 mg, 5.15 mmol) in 17 mL DMF were added acid **4** (1.41 g, 5.15 mmol) and *N*,*N*-diisopropylethylamine (DIEA) (2.04 mL, 11.7 mmol). After 5 min amine **9** (830 mg, 4.68 mmol; obtained from Boc-L-Ser(OBn)−OH) was added and the mixture was stirred at rt for 3.5 h. DMF was removed *in vacuo*, 20 mL water and 20 mL DCM were added, the phases were separated and the aq. solution was extracted twice with 20 mL DCM. The organic extracts were dried ($MgSO_4$) and the solvent evaporated. FC (hexane/EtOAc 2:1) gave 1.8 g (89%) of (*S*)-*N*-((*R*)-1-(benzyloxy)but-3-en-2-yl)-5-((*tert*-butyldimethylsilyl)oxy)octanamide as a slightly yellow oil. $[\alpha]_D^{20}$ = +2.7° (*c* 2.26, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.40−7.27 (m, 5H), 5.87 (ddd, *J* = 17.3, 10.4, 5.3 Hz, 1H), 5.78 (d, *J* = 8.5 Hz, 1H), 5.27−5.13 (m, 2H), 4.73−4.64 (m, 1H), 4.55 (d, *J* = 11.9 Hz, 1H), 4.51 (d, *J* = 11.3 Hz, 1H), 3.70−3.60 (m, 1H), 3.56 (d, *J* = 4.1 Hz, 2H), 2.19 (t, *J* = 7.6 Hz, 2H), 1.77−1.55 (m, 2H), 1.54−1.21 (m, 6H), 0.93−0.86 (m, 12H), 0.04 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): 172.3, 137.8, 136.0, 128.4, 127.8, 127.7, 115.9, 73.3, 71.79, 71.76, 50.8, 39.3, 37.0, 36.58, 36.55, 25.9, 21.64, 21.62, 18.4, 18.1, 14.3, −4.42, −4.45. IR: ν 3275, 3063, 2955, 2929, 2857, 2360, 2341, 1638, 1541, 1456, 1361, 1254, 1094, 1069, 1039, 920, 834, 773, 733, 696 cm^{-1}. HRMS (ESI) calcd for $[C_{25}H_{43}NO_3Si+H^+]$ 434.3085, found 434.3084.

A solution of the above (*S*)-*N*-((*R*)-1-(benzyloxy)but-3-en-2-yl)-5-((*tert*-butyldimethylsilyl)oxy)octanamide (1.70 g, 3.92 mmol) in DCM/TFA 4:1 (17 mL) was stirred for 2.5 h at 0 °C. Water (68 mL) was then added and the pH adjusted to 7 with sat. $NaHCO_3$. More water (30 mL) and DCM (120 mL) were added, the phases were separated and the aq. solution was extracted 4x with 120 mL DCM. The organic extracts were dried ($MgSO_4$) and the solvent was evaporated. FC (Et_2O/MeOH 98:2) gave 1.02 g (82%) of amide **10** as a colorless oil. $[\alpha]_D^{20}$ = +7.8° (*c* 0.81, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.41−7.27 (m, 5H), 6.00−5.77 (m, 2H), 5.28−5.13 (m, 2H), 4.74−4.63 (m, 1H), 4.54 (d, *J* = 12.0 Hz, 1H), 4.51 (d, *J* = 12.0 Hz, 1H), 3.61−3.52 (m, 3H), 2.31−2.15 (m, 2H), 1.81−1.69 (m, 3H), 1.55−1.24 (m, 6H), 0.96−0.86 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.5, 137.8, 135.8, 128.5, 127.8, 127.7, 116.0, 73.3, 71.8, 71.0, 70.9, 50.9, 39.7, 39.6 36.9, 36.4, 36.3, 21.6, 21.4, 18.8, 14.1. IR: ν 3291, 3064, 2956, 2930, 2870, 2360, 2342, 1637, 1541, 1455, 1361, 1124, 1028, 991, 921, 736, 697 cm^{-1}. HRMS (ESI) calcd for $[C_{19}H_{29}NO_3 + H^+]$ 320.2220, found 320.2218.

10 (obtained from amine **9** as derived from acetonide **15**): NMR, IR, and TLC data were identical with those reported above (major isomer). $[\alpha]_D^{20}$ = +39.6° (*c* 1.00, $CHCl_3$).

(*S*)-(*S*)-8-(((*R*)-1-(Benzyloxy)but-3-en-2-yl)amino)-8-oxooctan-4-yl-2-((*tert*-butoxycarbonyl)-(methyl)-amino)-3-phenyl-

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propanoate (12). To a solution of amide **10** (860 mg, 2.69 mmol) in 50 mL DCM were added Boc-*N*-Me-L-Phe-OH (**11**) (1.13 g, 4.04 mmol), DMAP (493 mg, 4.04 mmol), and DCC (1.67 g, 8.08 mmol) and the mixture was stirred at rt for 40 min. Silica gel (10 g) was then added and the solvent was evaporated. FC (hexane/EtOAc 1:1) gave 1.55 g of ester **12** (99%) as a colorless oil. $[\alpha]_D^{20} = -24.1°$ (*c* 0.50, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): Mixture of rotamers. δ 7.40–7.10 (m, 10H), 6.08–5.75 (m, 2H), 5.29–5.10 (m, 2H), 5.00–4.60 (m, 3H), 4.59–4.45 (m, 2H), 3.60–3.47 (m, 2H), 3.34–3.19 (m, 1H), 3.09–2.90 (m, 1H), 2.81–2.62 (m, 3H), 2.26–2.09 (m, 2H), 1.75–1.01 (m, 17H), 0.97–0.83 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.0, 171.8, 171.2, 170.9, 155.2, 153.3, 137.9, 137.6, 135.9, 128.9, 128.9, 128.49, 128.45, 128.3, 127.8, 127.7, 116.0, 80.2, 79.9, 77.4, 77.3, 77.1, 76.7, 74.6, 73.2, 71.7, 60.8, 60.0, 50.9, 36.1, 36.0, 35.2, 34.9, 34.0, 33.2, 32.3, 28.3, 28.2, 26.1, 25.7, 25.0, 24.7, 21.2, 18.5, 13.9. IR: ν 3308, 2978, 2932, 2871, 2360, 2342, 1733, 1698, 1653, 1541, 1456, 1393, 1365, 1142, 748, 697, 669 cm^{-1}. HRMS (ESI) calcd for $[C_{34}H_{48}N_2O_6 + Na^+]$ 603.3405, found 603.3405.

12 (obtained from amine **9** as derived from acetonide **15**): NMR, IR, and TLC data were identical with those reported above (major isomer). $[\alpha]_D^{20} = -13.5°$ (*c* 1.00, $CHCl_3$).

(*S*)-(*S*)-8-(((*R*)-1-(benzyloxy)but-3-en-2-yl)amino)-8-oxooctan-4-yl-2-(methylamino)-3-phenyl-propanoate (13). To a solution of **12** (1.55 g, 2.67 mmol) in 100 mL DCM were added triisopropylsilane (0.6 mL, 2.93 mmol) and 25 mL TFA. The mixture was stirred at rt for 30 min, cooled to 0 °C, and poured into 300 mL sat. $NaHCO_3$. DCM (300 mL) was added, the phases were separated and the aq. solution was extracted twice with 300 mL DCM. The extracts were dried ($MgSO_4$) and the solvent was evaporated. FC (hexane/EtOAc 1:1 + 1–2% Et_3N) to furnish 1.25 g (98%) of amine **13** as a yellow oil: $[\alpha]_D^{20} = +13.8°$ (*c* 1.00, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.40–7.14 (m, 10H), 5.93–5.77 (m, 2H), 5.25–5.13 (m, 2H), 4.93–4.82 (m, 1H), 4.71–4.62 (m, 1H), 4.55 (d, *J* = 11.7 Hz, 1H), 4.50 (d, *J* = 11.7 Hz, 1H), 3.55 (d, *J* = 5.2 Hz, 2H), 3.41 (t, *J* = 6.6 Hz, 1H), 2.98–2.86 (m, 2H), 2.36 (s, 3H), 2.12–2.05 (m, 2H), 1.59–1.18 (m, 8H), 0.87 (t, *J* = 8.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.4, 171.88, 171.86, 137.8, 137.3, 135.95, 135.91, 129.3, 128.5, 128.4, 127.72, 127.70, 126.6, 116.0, 115.97, 74.21, 74.16, 73.29, 73.26, 71.77, 71.75, 65.0, 64.9, 50.9, 39.6, 36.2, 35.94, 35.92, 34.7, 33.19, 33.15, 21.1, 21.0, 18.6, 13.9. IR: ν 3291, 2957, 2933, 2871, 2360, 2341, 1725, 1647, 1541, 1455, 1362, 1178, 1130, 921, 739, 698 cm^{-1}. HRMS (ESI) calcd for $[C_{29}H_{39}N_2O_4 + H^+]$ 481.3061, found 481.3067.

13 (obtained from amine **9** as derived from acetonide **15**): NMR, IR, and TLC data were identical with those reported above (major isomer). $[\alpha]_D^{20} = +42.9°$ (*c* 1.00, $CHCl_3$).

(*S*)-(*S*)-8-(((*R*)-1-(Benzyloxy)but-3-en-2-yl)amino)-8-oxooctan-4-yl-2-((*S*)-*N*,2-dimethylpent-4-enamido)-3-phenylpropanoate (14). To a solution of acid **6** (164 mg, 1.44 mmol) and HATU (546 mg, 1.44 mmol) in 10 mL DMF was added DIEA (0.5 mL, 2.87 mmol). After 5 min at rt amine **13** (460 mg, 0.96 mmol) was added and the solution was stirred at rt for 3 h. After removal of DMF, 20 mL DCM and 20 mL 10% MeCN/water were added. The phases were separated, the aq. solution was extracted twice with 20 mL DCM and the organic extracts were dried ($MgSO_4$) and the solvent evaporated. FC (hexane/EtOAc 1:1 + 2% Et_3N) gave 510 mg (92%) of amide **14** as a yellow oil. $[\alpha]_D^{20} = -19.9°$ (*c* 1.28, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.42–7.08 (m, 10H), 6.24–6.07 (m, 1H), 5.94–5.63 (m, 2H), 5.31–4.61 (m, 5H), 4.60–4.45 (m, 2H), 3.55 (d, *J* = 5.0 Hz, 2H), 3.42–3.21 (m, 1H), 3.07–2.75 (m, 4H), 2.66–2.52 (m, 1H), 2.45–2.32 (m, 1H), 2.28–2.10 (m, 2H), 2.07–1.79 (m, 2H), 1.71–0.98 (m, 10H), 0.94–0.72 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.3, 172.4, 170.7, 137.9, 137.2, 136.2, 135.9, 129.1, 128.9, 128.8, 128.5, 128.4, 128.3, 127.8, 127.7, 126.8, 116.3, 116.0, 77.4, 77.1, 76.7, 74.8, 74.7, 73.2, 71.8, 58.7, 50.9, 37.8, 36.14, 36.10, 35.7, 34.8, 33.3, 33.1, 21.33, 21.28, 18.6, 16.8, 13.9. IR: ν 3308, 3063, 2959, 2932, 2871, 2360, 2341, 1733, 1636, 1541, 1456, 1129, 1088, 917, 740, 698 cm^{-1}. HRMS (ESI) calcd for $[C_{35}H_{48}N_2O_5 + Na^+]$ 599.3455, found 599.3464.

14 (obtained from amine **9** as derived from acetonide **15**): NMR, IR, and TLC data were identical with those reported above. $[\alpha]_D^{20} = +12.9°$ (*c* 1.00, $CHCl_3$).

Haliclamide (1). A solution of diene **14** (300 mg, 0.52 mmol) in 150 mL toluene was refluxed with Grubbs second generation catalyst (66 mg, 0.08 mmol) for 22 h. After solvent removal the residue was submitted to FC in DCM/acetone 5:1 (column diameter 2 cm, column length 15 cm, 15 fractions of 12 mL each). Fractions 9–41 were repurified by FC with DCM/acetone 5:1 + 0.5% MeOH to give 130 mg (46%) of a multicomponent mixture as a brown resin: ^1H NMR (400 MHz, $CDCl_3$): δ 7.40–7.10 (m, 10H), 6.02–5.85 (m, 1H), 5.59–5.37 (m, 1H), 5.04–4.84 (m, 1H), 4.73–4.60 (m, 1H), 4.56–4.44 (m, 2H), 3.52–3.37 (m, 2H), 2.95–2.76 (m, 4H), 2.65–2.23 (m, 3H), 2.16–1.98 (m, 2H), 1.84–1.39 (m, 6H), 1.39–1.19 (m, 3H), 0.97–0.80 (m, 3H), 0.76–0.58 (m, 3H). HRMS (ESI) calcd for $[C_{33}H_{44}N_2O_5 + H^+]$ 549.3323, found 549.3314.

The above material (70 mg, 0.13 mmol (based on the molecular weight of the structure of the RCM product from diene **14**)) was hydrogenated over Pd–C (27 mg) in 12 mL MeOH at 3 bar of hydrogen pressure for 18 h. The suspension was filtered and the solvent evaporated. FC on silica gel 60 (20–45 μm) (DCM/acetone 7:3 + 3% MeOH) gave 22.5 mg (38%) of an inseparable 92/8 mixture of haliclamide (**1**) and **1**-***SR***, and 19 mg (32%) of a 9/1/15 mixture of haliclamide (**1**), **1**-***SR***, and 14*S* haliclamide, respectively, as amorphous white solids. **Haliclamide (1):** $[\alpha]_D^{24}$: −4.1° (*c* 0.02, $CHCl_3$) (lit.:[2] $[\alpha]_D^{24}$: −4.8° (*c* 0.006 g/mL, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ 7.32–7.12 (m, 5H), 6.83 (d, *J* = 5.7 Hz, 1H), 5.90 (dd, *J* = 11.9, 5.3 Hz, 1H), 5.16 (br s, 1H), 5.02–4.95 (m, 1H), 3.87 (dd, *J* = 12.1, 1.8 Hz, 1H), 3.73–3.66 (m, 1H), 3.51 (dd, *J* = 14.7, 4.7 Hz, 1H), 3.45–3.37 (m, 1H), 2.95 (dd, *J* = 15.1, 12.0 Hz, 1H), 2.84 (s, 3H), 2.65–2.57 (m, 1H), 2.47–2.40 (m, 1H), 2.20–2.10 (m, 2H), 1.84–1.68 (m, 2H), 1.67–1.39 (m, 6H), 1.38–1.14 (m, 4H), 1.11–1.01 (m, 1H), 0.93 (t, *J* = 7.4 Hz, 3H), 0.65 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): 178.2, 174.4, 170.7, 136.6, 128.5, 128.4, 126.8, 76.7, 65.7, 56.3, 53.6, 37.1, 36.41, 36.37, 34.2, 32.0, 31.4, 31.2, 27.8, 23.2, 22.9, 18.5, 18.0, 14.0. HRMS (ESI) calcd for $[C_{26}H_{40}N_2O_5 + H^+]$ 461.3010, found 461.3016.

(*S*)-4-((4-Methoxybenzyl)oxy)butane-1,2-diol (16). To a solution of PMB ether **15**[34,35] (217 mg, 0.82 mmol) in 15 mL MeOH was added $CuCl_2 \bullet 2H_2O$ (750 mg, 4.5 mmol) and the mixture was refluxed for 2 h. After cooling to 0 °C, $NaHCO_3$ was added and the solvent was evaporated. The residue was treated with EtOAc and filtered and the filtrate was concentrated. FC (EtOAc) gave 170 mg (92%) of monoprotected triol **16** as a clear oil. $[\alpha]_D^{25} = +5.4°$ (*c* 1.0, $CHCl_3$) (lit.:[34] $[\alpha]_D^{25} = +4.4°$ (*c* 0.8, $CHCl_3$)). ^1H NMR (400 MHz, $CDCl_3$): δ 7.23–7.11 (m, 2H), 6.89–6.75 (m, 2H), 4.39 (*s*, 2H), 3.89–3.78 (m, 1H), 3.73 (s, 3H), 3.65–3.49 (m, 3H), 3.47–3.36 (m, 1H), 3.05 (br s, 1H), 2.25 (br s, 1H), 1.83–1.58 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.4, 129.8, 129.4, 113.9, 73.0, 71.4, 68.0, 66.6, 55.3, 32.8. HRMS (ESI) calcd for $[C_{12}H_{18}O_4 + Na^+]$ 249.1097, found 249.1098.

(*S*)-1-(Benzyloxy)-4-((4-methoxybenzyl)oxy)butan-2-ol (17). A suspension of monoprotected triol **16** (2.0 g, 8.8 mmol) and Bu_2SnO (2.41 g, 9.7 mmol) in 20 mL benzene was refluxed for 24 h (Dean–Stark trap). TBAI (3.58 g, 9.7 mmol) and BnCl (1.11 mL, 9.7 mmol) were then added and refluxing was continued for 3 h. After cooling to rt EtOAc was added (30 mL), the phases were separated and the EtOAc solution was washed twice with each 15 mL NH_4Cl and 15 mL brine. The solvent was evaporated. FC (hexane/Et_2O 1:1) gave 2.42 g (87%) of **17** as a clear oil. $[\alpha]_D^{25} = -12.0°$ (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.41–7.24 (m, 7H), 6.93–6.87 (m, 2H), 4.58 (s, 2H), 4.46 (s, 2H), 4.09–3.99 (m, 1H), 3.82 (s, 3H), 3.72–3.59 (m, 2H), 3.53–3.40 (m, 2H), 2.99 (d, *J* = 3.3 Hz, 1H), 1.84–1.78 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.1, 138.1, 130.2, 129.2, 128.3, 127.59, 127.56, 113.7, 74.3, 73.2, 72.7, 69.1, 67.5, 55.1, 33.1. HRMS (ESI) calcd for $[C_{19}H_{24}O_4 + H^+]$ 317.1747, found 317.1744.

(*R*)-2-(1-(Benzyloxy)-4-((4-methoxybenzyl)oxy)butan-2-yl)-isoindoline-1,3-dione (18). To a solution of **17** (91 mg, 0.28 mmol), phthalimide (84 mg, 0.57 mmol), and PPh_3 (150 mg, 0.57

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mmol) in 5 mL THF was added diisopropyl azodicarboxylate (DIAD) (112 μL, 0.57 mmol) at 0 °C. The mixture was stirred overnight at rt and the solvent evaporated. FC (hexane/EtOAc 3:1) gave 121.6 mg (95%) of phthalimide **18** as a clear oil. $[\alpha]_D^{20}$ = +0.47° (*c* 1.00, $CHCl_3$).[43] ^1H NMR (400 MHz, $CDCl_3$): δ 7.83−7.77 (m, 2H), 7.73−7.67 (m, 2H), 7.31−7.21 (m, 5H), 7.18−7.12 (m, 2H), 6.80−6.75 (m, 2H), 4.75 (ddt, *J* = 9.8, 5.4, 4.5 Hz, 1H), 4.54 (d, *J* = 11.9 Hz, 1H), 4.45 (d, *J* = 12.1 Hz, 1H), 4.30 (*s*, 2H), 4.00 (dd, *J* = 9.9, 9.3 Hz, 1H), 3.78 (*s*, 3H), 3.72 (dd, *J* = 10.1, 5.6 Hz, 1H), 3.57−3.40 (m, 2H), 2.36 (dddd, *J* = 14.5, 10.3, 6.0, 4.5 Hz, 1H), 2.00 (tdd, *J* = 14.5, 7.8, 4.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.6, 159.0, 138.0, 133.7, 132.0, 130.2, 129.2, 128.3, 127.6, 127.5, 123.1, 113.6, 72.8, 72.7, 69.7, 67.0, 55.2, 48.9, 28.8. IR: ν 2928, 2863, 1773, 1751, 1734, 1708, 1611, 1513, 1468, 1455, 1376, 1337, 1303, 1289, 1248, 1173, 1146, 1098, 1036, 820, 741, 721, 699 cm^{-1}. HRMS (ESI) calcd for $[C_{27}H_{27}NO_5 + H^+]$ 446.1962, found 446.1961.

(*R*)-Methyl 5-hydroxyoctanoate (*ent*-3). To a solution of (+)-$(Ipc)_2BCl$ (7.49 g, 23.3 mmol) in 50 mL Et_2O was added a 1 M solution of allylmagnesium bromide (17.0 mL, 17 mmol) in Et_2O dropwise at 0 °C. The mixture was allowed to warm to rt and was then cooled to −100 °C. A solution of methyl 5-oxopentanoate (**2**) (2.09 g, 16.1 mmol) in 20 mL Et_2O was added dropwise strictly at −100 °C. The mixture was then stirred at −100 °C for another hour; 3 mL dry MeOH were added and the mixture was allowed to warm to rt. Three M NaOH (8.5 mL) and 30% H_2O_2 (10 mL) were added and the mixture was stirred for one hour at rt. It was then extracted twice with 70 mL Et_2O, the combined organic extracts were washed with 100 mL of brine and dried over $MgSO_4$, and the solvent was evaporated. FC of the residue (DCM/acetone/MeOH 97:2:1) gave 1.40 g (53%) of (*S*)-methyl 5-hydroxyoct-7-enoate (er 9:1) as a clear oil. $[\alpha]_D^{20}$ = −6.3° (*c* 1.03, $CHCl_3$) (lit.[12] ((+)-enantiomer). $[\alpha]_D$ = +4.55° (*c* 1.67, $CHCl_3$)). ^1H NMR (400 MHz, $CDCl_3$): δ 5.88−5.77 (m, 1H), 5.18−5.12 (m, 2H), 3.70−3.62 (m, 4H), 2.39−2.27 (m, 3H), 2.21−2.12 (m, 1H), 1.91−1.39 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.1, 134.6, 118.2, 70.2, 51.5, 41.9, 36.0, 33.8, 21.0. IR: ν 3425, 3079, 2952, 2928, 2358, 1723, 1641, 1436, 1160 cm^{-1}. HRMS (ESI) calcd for $[C_9H_{16}O_3+Na^+]$ 195.0992, found 195.0993.

(*S*)-Methyl 5-hydroxyoct-7-enoate (3.57 g, 21 mmol) was hydrogenated over 1 g of Ra−Ni in 100 mL EtOAc/MeOH 1:1 for 3 h at rt at atmospheric pressure. The catalyst was removed by filtration and the filtrate was evaporated. Water (50 mL) was then added and the mixture extracted 3× with 50 mL of EtOAc. The combined organic phases were dried over $MgSO_4$ and the solvent removed by evaporation to yield 2.70 g (75%) of ***ent*-3** as a clear oil. $[\alpha]_D^{20}$ = −0.14° (*c* 1.03, $CHCl_3$) (lit.[12] (**3**): $[\alpha]_D$ = +1.29° (*c* 1.25, $CHCl_3$)). ^1H NMR (400 MHz, $CDCl_3$): δ 3.68 (s, 3H), 3.65−3.56 (m, 1H), 2.36 (t, *J* = 7.3 Hz, 2H), 1.84−1.64 (m, 2H), 1.56−1.31 (m, 7H), 0.93 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.2, 70.9, 51.4, 39.6, 36.6, 33.8, 20.9, 18.7, 14.0. IR: ν 2922, 2852, 2337, 1731, 1247, 1050 cm^{-1}. HRMS (ESI) calcd for $[C_9H_{18}O_3 + Na^+]$ 197.1148, found 197.1155.

(*R*)-5-((tert-Butyldimethylsilyl)oxy)octanoic acid (*ent*-4). To a solution of ***ent*-3** (2.38 g, 13.7 mmol) and imidazole (2.26 g, 34.2 mmol) in 20 mL dry DCM was added TBSCl (3.18 g, 20.5 mmol) 0 °C and the mixture was stirred at rt overnight. It was then poured into a mixture of 300 mL Et_2O and 300 mL of brine. The phases were separated and the aq. phase was twice extracted with 250 mL Et_2O. The combined organic extracts were dried over $MgSO_4$, the solvent evaporated, and the residue was purified by FC (hexane/EtOAc 9:1) to give 3.17 g (81%) of (*R*)-methyl 5-((*tert*-butyldimethylsilyl)oxy)-octanoate as clear oil. $[\alpha]_D^{20}$ = −1.21° (*c* 0.88, $CHCl_3$).[43] ^1H NMR (400 MHz, $CDCl_3$): δ 3.70−3.63 (m, 4H), 2.30 (t, *J* = 7.4 Hz, 2H), 1.76−1.59 (m, 2H), 1.49−1.24 (m, 6H), 0.91−0.88 (m, 12H), 0.05 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.1, 71.7, 51.4, 39.3, 36.4, 34.3, 25.90, 20.8, 18.5, 18.1, 14.3, −4.46, −4.48. IR: ν 2955, 2930, 2857, 2360, 1742, 1252, 1069 cm^{-1}. HRMS (ESI) calcd for $[C_{15}H_{32}O_3Si + Na^+]$ 311.2013, found 311.2011.

A solution of the above (*R*)-methyl 5-((*tert*-butyldimethylsilyl)oxy) octanoate (1.78 g, 6.2 mmol) in 50 mL THF/water 4:1 was stirred together with LiOH (711 mg, 9.7 mmol) at rt for 17 h. At this point additional LiOH (727 mg, 9.9 mmol) was added and stirring was continued for 3.5 h. THF was then removed by evaporation, 15 mL water were added, and the pH was adjusted to 4 with 1 M HCl. The solution was then extracted twice with 100 mL DCM, the combined organic extracts were dried over $MgSO_4$ and the solvent was evaporated to yield 1.65 g (97%) ***ent*-4** as a clear oil: $[\alpha]_D^{20}$ = −0.67° (*c* 1.16, $CHCl_3$).[43] ^1H NMR (400 MHz, $CDCl_3$): δ 10.10 (br s, 1H), 3.70−3.63 (m, 1H), 2.36 (t, *J* = 7.4 Hz, 2H), 1.76−1.59 (m, 2H), 1.51−1.24 (m, 6H), 0.92−0.86 (m, 12H), 0.05 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.7, 71.7, 39.3, 36.3, 34.3, 25.9, 20.5, 18.5, 18.1, 14.3, −4.46, −4.49. IR: ν 2956, 2860, 2360, 1708, 1254, 1140 cm^{-1}. HRMS (ESI) calcd for $[C_{14}H_{30}O_3Si + Na^+]$ 297.1856, found 297.1855.

(*R*)-*N*-((*R*)-1-(Benzyloxy)but-3-en-2-yl)-5-((*tert*-butyldimethylsilyl)oxy)octanamide. To a solution of HBTU (924 mg, 2.44 mmol) in 8 mL dry DMF were added ***ent*-4** (668 mg, 2.51 mmol) and DIEA (0.96 mL, 5.5 mmol) and the mixture stirred for 5 min. Then **9** (388 mg, 2.19 mmol) was added and stirring was continued for 3 h at rt. The DMF was removed by evaporation, 60 mL water 10% MeCN and 60 mL DCM were added and the phases were separated. The aq. phase was extracted twice with 60 mL DCM. The combined organic extracts were dried over $MgSO_4$ and the solvent was evaporated. FC (hexane/EtOAc 2:1) gave 811 mg (85%) of (*R*)-*N*-((*R*)-1-(benzyloxy)but-3-en-2-yl)-5-((*tert*-butyldimethylsilyl)-oxy)-octanamide as an amorphous white solid. $[\alpha]_D^{20}$ = +14.0° (*c* 0.91, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.39−7.29 (m, 5H), 5.88 (ddd, *J* = 17.3, 10.5, 5.3 Hz, 1H), 5.79 (d, *J* = 8.2 Hz, 1H), 5.26−5.16 (m, 2H), 4.72−4.66 (m, 1H), 4.56 (d, *J* = 12.0 Hz, 1H), 4.52 (d, *J* = 12.1 Hz, 1H), 3.69−3.62 (m, 1H), 3.56 (d, *J* = 4.2 Hz, 2H), 2.19 (t, *J* = 7.6 Hz, 2H), 1.76−1.60 (m, 2H), 1.49−1.31 (m, 6H), 0.90−0.86 (m, 12H), 0.05 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): 172.3, 137.9, 136.0, 128.5, 127.8, 127.7, 115.9, 73.3, 71.8, 50.8, 39.3, 37.0, 36.58, 36.56, 25.9, 21.64, 21.62, 18.4, 18.1, 14.3, −4.42, −4.46. IR: ν 3285, 3070, 2955, 2929, 2857, 1639, 1540, 1361, 1092 cm^{-1}. HRMS (ESI) calcd for $[C_{25}H_{43}NO_3Si + H^+]$ 434.3085, found 434.3088.

(*R*)-*N*-((*R*)-1-(Benzyloxy)but-3-en-2-yl)-5-hydroxyoctanamide. A solution of (*R*)-*N*-((*R*)-1-(benzyloxy)but-3-en-2-yl)-5-((*tert*-butyldimethylsilyl)-oxy)octanamide (838 mg, 1.93 mmol) in 1.7 mL TFA and 6.7 mL dry DCM was stirred at 0 °C for 3.5 h. A total of 35 mL of water was added and the pH was adjusted to 7 with sat. $NaHCO_3$. Then 30 mL DCM were added, the phases were separated and the aq. phase was extracted 4× with 30 mL DCM. The combined organic phases were then dried over $MgSO_4$ and the solvent was evaporated. FC (Et_2O/MeOH 98:2) gave 508 mg (82%) of (*R*)-*N*-((*R*)-1-(benzyloxy)but-3-en-2-yl)-5-hydroxyoctanamide as a colorless oil. $[\alpha]_D^{20}$ = +17.3° (*c* 0.70, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.39−7.28 (m, 5H), 5.99−5.80 (m, 2H), 5.27−5.16 (m, 2H), 4.73−4.66 (m, 1H), 4.56 (d, *J* = 12.0 Hz, 1H), 4.52 (d, *J* = 12.1 Hz, 1H), 3.64−3.54 (m, 3H), 2.31−2.16 (m, 2H), 1.83−1.71 (m, 3H), 1.52−1.18 (m, 7H), 0.96−0.86 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.6, 137.7, 135.8, 128.4, 127.8, 127.7, 116.0, 73.2, 71.7, 70.9, 70.8, 50.8, 39.7, 39.6, 36.6, 36.31, 36.26, 21.5, 21.4, 18.8, 14.0. IR: ν 3293, 2957, 2931, 2869, 2362, 1638, 1541, 1455, 1362, 1104 cm^{-1}. HRMS (ESI) calcd for $[C_{19}H_{30}NO_3 + Na^+]$ 342.2040, found 342.2037.

(*S*)-(*R*)-8-(((*R*)-1-(Benzyloxy)but-3-en-2-yl)amino)-8-oxooctan-4-yl-2-((*tert*-butoxycarbonyl)-(methyl)-amino)-3-phenylpropanoate. To a solution of (*R*)-*N*-((*R*)-1-(benzyloxy)but-3-en-2-yl)-5-hydroxyoctanamide (462 mg, 1.45 mmol) in 25 mL DCM were added Boc-*N*-Me-Phe-OH (**11**) (603 mg, 2.16 mmol), DMAP (272 mg, 2.23 mmol), and DCC (0.90 g, 4.37 mmol) and the mixture was stirred at rt for 3 h. Then 4 g silica gel were added and the solvent was removed by evaporation. FC (hexane/EtOAc 1:1) yielded 831 mg (99%) of (*S*)-(*R*)-8-(((*R*)-1-(benzyloxy)but-3-en-2-yl)amino)-8-oxooctan-4-yl-2-((tert-butoxycarbonyl)-(meth-yl)-amino)-3-phenylpropanoate as a colorless oil. $[\alpha]_D^{24}$ = −10.4° (*c* 1.57, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.39−7.15 (m, 10H), 6.05−5.82 (m, 2H), 5.29−5.15 (m, 2H), 4.98−4.84 (m, 2H), 4.73−4.64 (m, 1H), 4.56 (d, *J* = 12.1 Hz, 1H), 4.52 (d, *J* = 12.1 Hz, 1H), 3.55 (d, *J* = 4.4 Hz, 2H), 3.34−3.23 (m, 1H), 3.08−2.90 (m, 1H), 2.81−2.62 (d, *J* = 16.3 Hz, 3H), 2.27−2.13 (m, 2H), 1.74−1.43 (m, 6H), 1.42−1.12 (m, 11H), 0.95−0.84 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.1,

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171.8, 171.4, 170.9, 155.8, 137.9, 137.6, 135.9, 128.9, 128.5, 128.4, 127.8, 127.7, 116.0, 80.2, 79.9, 75.0, 74.7, 73.2, 71.7, 60.8, 59.8, 50.9, 36.2, 36.1, 35.9, 35.1, 34.9, 33.4, 33.2, 32.1, 28.3, 28.2, 25.0, 21.3, 18.5, 13.9. IR: ν 3304, 2960, 2933, 2870, 2361, 2336, 1732, 1652, 1454, 1365, 1141 cm^{-1}. HRMS (ESI) calcd for [$C_{34}H_{48}N_2O_6$ + Na^+] 603.3405, found 603.3394.

(*S*)-(*R*)-8-(((*R*)-1-(Benzyloxy)but-3-en-2-yl)amino)-8-oxooctan-4-yl-2-(methylamino)-3-phenyl-propanoate. To a solution of (*S*)-(*R*)-8-(((*R*)-1-(benzyloxy)but-3-en-2-yl)amino)-8-oxooctan-4-yl 2-((tert-butoxycarbonyl)-(methyl)-amino)-3-phenyl-propanoate (735 mg, 1.23 mmol) in 40 mL DCM were added TIPS (290 μL, 1.42 mmol) and 10 mL TFA and the mixture was stirred at rt for 30 min. After cooling to 0 °C it was poured into 150 mL sat. $NaHCO_3$, 150 mL DCM were added and the phases were separated. The aq. phase was extracted twice with 150 mL DCM, the combined organic phases were dried over $MgSO_4$, and the solvent was evaporated. FC (hexane/EtOAc 1:1 + 2% Et_3N) gave 602 mg (99%) of (*S*)-(*R*)-8-(((*R*)-1-(benzyloxy)but-3-en-2-yl)amino)-8-oxooctan-4-yl-2-(methylamino)-3-phenyl-propanoate as clear viscous oil. $[\alpha]_D^{24}$ = +23.4° (*c* 0.48, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39−7.18 (m, 10H), 5.92−5.80 (m, 2H), 5.32−5.14 (m, 3H), 4.93−4.83 (m, 1H), 4.71−4.63 (m, 1H), 4.55 (d, *J* = 12.1 Hz, 1H), 4.51 (d, *J* = 12.1 Hz, 1H), 3.55 (d, *J* = 4.2 Hz, 2H), 3.42 (t, *J* = 7.1 Hz, 1H), 2.92 (d, *J* = 7.0 Hz, 2H), 2.36 (s, 3H), 2.23−2.10 (m, 2H), 1.71−1.29 (m, 6H), 1.18−1.02 (m, 2H), 0.82 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.4, 171.89, 171.84, 137.8, 137.3, 135.91, 129.3, 129.2, 128.5, 128.4, 127.9, 127.7, 126.7, 116.0, 74.2, 73.3, 71.8, 64.9, 64.8, 50.9, 39.6, 39.5, 36.2, 35.9, 34.7, 33.3, 33.2, 21.4, 21.0, 18.6, 18.3, 13.94, 13.91. IR: ν 3312, 2935, 2870, 2358, 1725, 1642, 1540, 1455, 1362, 1254, 1179, 1114 cm^{-1}. HRMS (ESI) calcd for [$C_{29}H_{40}N_2O_4$+Na^+] 503.2880, found 503.2874.

(*S*)-(*R*)-8-(((*R*)-1-(Benzyloxy)but-3-en-2-yl)amino)-8-oxooctan-4-yl-2-((*S*)-*N*,2-dimethylpent-4-enamido)-3-phenylpropanoate. To a solution of **6** (72 mg, 0.63 mmol) and HATU (239 mg, 0.63 mmol) in 3.7 mL dry DMF was added DIEA (0.2 mL, 1.15 mmol) and the mixture was stirred for 5 min at rt. Then (*S*)-(*R*)-8-(((*R*)-1-(benzyloxy)but-3-en-2-yl)amino)-8-oxooctan-4-yl-2-(methylamino)-3-phenyl-propanoate (196 mg, 0.41 mmol) was added and the resulting solution was stirred at rt for 4 h. After removal of DMF 7.5 mL DCM and 7.5 mL 10% MeCN in water were added and the phases were separated. The aq. phase was extracted twice with 7.5 mL DCM, the combined organic extracts were dried over $MgSO_4$, and the solvent was evaporated. FC (hexane/EtOAc 1:1 + 2% Et_3N) yielded 180 mg (77%) of (*S*)-(*R*)-8-(((*R*)-1-(benzyloxy)but-3-en-2-yl)amino)-8-oxooctan-4-yl 2-((*S*)-*N*,2-dimethylpent-4-enamido)-3-phenylpropanoate as yellowish resin. $[\alpha]_D^{24}$ = −9.6° (*c* 0.48, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41−7.10 (m, 10H), 6.20−5.65 (m, 3H), 5.35−5.15 (m, 3H), 5.05−4.60 (m, 4H), 4.59−4.49 (m, 2H), 3.62−3.52 (m, 2H), 3.44−3.25 (m, 1H), 3.09−2.94 (m, 1H), 2.93−2.81 (m, 3H), 2.70−2.55 (m, 1H), 2.45−2.34 (m, 1H), 2.32−2.13 (m, 2H), 2.09−1.80 (m, 2H), 1.75−1.40 (m, 6H), 1.39−1.11 (m, 2H), 1.08−0.74 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.4, 172.1, 171.0, 137.9, 137.1, 136.2, 135.97, 135.92, 128.9, 128.44, 128.37, 127.7, 116.4, 116.0, 74.7, 73.20, 73.16, 71.8, 58.4, 51.0, 50.93, 50.88, 37.8, 36.2, 35.8, 35.7, 34.9, 33.3, 33.1, 21.4, 18.5, 16.8, 14.0, 13.9. IR: ν 3311, 3069, 3029, 2954, 2868, 2330, 1732, 1637, 1090 cm^{-1}. HRMS (ESI) calcd for [$C_{35}H_{48}N_2O_5$ + Na^+] 599.3455, found 599.3454.

(3*S*,6*S*,10*R*,16*R*)-3-Benzyl-10-(hydroxymethyl)-4,6-dimethyl-16-propyl-1-oxa-4,11-diazacyclo-hexadecane-2,5,12-trione (1-*SR*). A solution of (*S*)-(*R*)-8-(((*R*)-1-(benzyloxy)but-3-en-2-yl)-amino)-8-oxooctan-4-yl 2-((*S*)-*N*,2-dimethylpent-4-enamido)-3-phenylpropanoate (132 mg, 0.23 mmol) in 66 mL toluene was refluxed with Grubbs II catalyst (28.6 mg, 0.03 mmol) for 16 h. After solvent removal the residue was submitted to FC in hexane/EtOAc 1:2 to yield 30 mg (24%) of (3*S*,6*S*,10*R*,16*R*)-3-benzyl-10-((benzyloxy)-methyl)-4,6-dimethyl-16-propyl-1-oxa-4,11-diazacyclohexadec-8-ene-2,5,12-trione as a brown resin. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34−7.02 (m, 10H), 5.77−5.54 (m, 1H), 5.37−5.20 (m, 1H), 5.00−4.77 (m, 1H), 4.51−4.34 (m, 2H), 4.28−3.74 (m, 2H), 3.63−3.14 (m, 2H), 3.06−2.55 (m, 5H), 2.34−2.03 (m, 3H), 1.99−0.96 (m, 11H), 0.90−0.64 (m, 6H). HRMS (ESI) calcd for [$C_{33}H_{44}N_2O_5$ + H^+] 549.3323, found 549.3316.

A solution of the above material (30 mg, 0.055 mmol) in 6 mL MeOH was hydrogenated over Pd−C (15 mg, 0.014 mmol) at 3 bar for 21 h. Additional Pd−C (7.8 mg, 0.007 mmol) was added and hydrogenation was continued for 40 h. The suspension was filtered, the filtrate was evaporated, and the residue was purified by FC (DCM/acetone 7:3 + 3% MeOH) on silica gel 60 (20−45 μm) to yield 4 mg (16%) of **1-*SR*** as an amorphous white solid and 18 mg (72%) of a 2:1 mixture of **1-*SR*** and 14*S*-**1-*SR***. **1-*SR***: $[\alpha]_D^{24}$ = +49.9° (*c* 0.16, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.24−7.10 (m, 5H), 6.00 (d, *J* = 6.8 Hz, 1H), 5.66 (dd, *J* = 11.7, 5.7 Hz, 1H), 4.95−4.89 (m, 1H), 3.72−3.55 (m, 3H), 3.55−3.46 (m, 1H), 3.29 (dd, *J* = 15.1, 5.6 Hz, 1H), 2.95 (dd, J= 15.3, 11.7 Hz, 1H), 2.94 (*s*, 3H), 2.73−2.63 (m, 1H), 2.33 (td, *J* = 12.7, 3.8 Hz, 1H), 2.09−1.99 (m, 1H), 1.77−1.11 (m, 14H), 0.85−0.78 (m, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): 177.7, 174.8, 173.5, 136.1, 128.6, 128.3, 126.9, 73.7, 66.8, 55.7, 52.4, 36.8, 36.4, 35.1, 34.7, 34.2, 32.8, 31.0, 29.6, 23.1, 22.8, 18.8, 18.1, 13.8. (Single isomer). IR: ν 3308, 2929, 1730, 1649, 1541, 1458, 670 cm^{-1}. HRMS (ESI) calcd for [$C_{26}H_{40}N_2O_5$ + H^+] 461.3010, found 461.3015.

(*R*)-2-Methylpent-4-enoic acid (*ent*-6). To a solution of (*S*)-4-benzyl-3-((*R*)-2-methylpent-4-enoyl)-oxazolidin-2-one (6.24 g, 22.8 mmol) in 60 mL THF/water 4:1 was added LiOH (2.18 g, 91.2 mmol) and 50% H_2O_2 (2.90 mL, 50.2 mmol) and the mixture was stirred at rt overnight. The pH was then adjusted to 1−2 with 90 mL 1 M HCl and the mixture was extracted thrice with 300 mL Et_2O. The combined organic extracts were dried over $MgSO_4$ and the solvent was removed. The product was distilled under reduced pressure to yield ***ent*-6** (1.91 g, 73%) as a colorless liquid. $[\alpha]_D^{20}$ = −10.3° (*c* 1.92, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.17 (s br, 1H), 5.77−5.63 (m, 1H), 5.07−4.94 (m, 2H), 2.56−2.43 (m, 1H), 2.43−2.31 (m, 1H), 2.20−2.09 (m, 1H), 1.12 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 182.6, 135.1, 117.2, 39.1, 37.4, 16.3. IR: ν 2979, 2666, 1703, 1643, 1417, 1244, 916 cm^{-1}. HRMS (ESI) calcd for [$C_6H_9O_2$ − H^+] 113.0608, found 113.0608.

(*S*)-(*S*)-8-(((*R*)-1-(Benzyloxy)But-3-en-2-yl)amino)-8-oxooctan-4-yl-2-((*R*)-*N*,2-dimethylpent-4-enamido)-3-phenylpropanoate. To a solution of ***ent*-6** (191 mg, 1.67 mmol) and HATU (635 mg, 1.67 mmol) in 10 mL dry DMF was added DIEA (0.6 mL, 3.34 mmol) and the mixture stirred for 5 min at rt. Then **13** (535 mg, 1.11 mmol) was added and the resulting solution was stirred at rt for 5 h. After removal of DMF 20 mL DCM and 20 mL 10% MeCN in water were added. The phases were separated and the aq. solution was extracted twice with 20 mL DCM. The combined organic extracts were dried over $MgSO_4$ and the solvent was evaporated. FC (hexane/EtOAc 1:1 + 2% Et_3N) gave 630 mg (98%) of (*S*)-(*S*)-8-(((*R*)-1-(benzyloxy)but-3-en-2-yl)amino)-8-oxooctan-4-yl-2-((*R*)-*N*,2-dimethylpent-4-enamido)-3-phenylpropanoate as dark yellow oil. $[\alpha]_D^{20}$ = −41.6° (*c* 1.01, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38−7.12 (m, 10H), 6.30−6.19 (m, 1H), 5.93−5.81 (m, 1H), 5.45−5.33 (m, 1H), 5.32−5.14 (m, 3H), 5.02−4.80 (m, 3H), 4.74−4.62 (m, 1H), 4.58−4.48 (m, 2H), 3.56 (d, *J* = 5.0 Hz, 2H), 3.38 (dd, *J* = 14.7, 5.7 Hz, 1H), 3.09−3.00 (m, 1H), 2.88−2.76 (m, 3H), 2.63−2.53 (m, 1H), 2.27−2.11 (m, 3H), 1.94−1.77 (m, 1H), 1.74−1.16 (m, 8H), 1.05 (d, *J* = 7.0 Hz, 3H), 0.90 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.4, 172.3, 172.2, 170.7, 137.9, 137.2, 136.96, 136.92, 128.9, 128.4, 127.70, 127.67, 116.2, 116.0, 115.9, 74.79, 74.75, 73.2, 71.8, 71.7, 61.8, 58.7, 50.9, 38.6, 37.8, 36.10, 35.8, 34.6, 33.1, 29.7, 21.4, 21.3, 18.6, 18.5, 16.9, 16.6, 14.0. IR: ν 3310, 3064, 2974, 2933, 2871, 2360, 2341, 1732, 1636, 1541, 1456, 1129, 1089, 917, 738, 698 cm^{-1}. HRMS (ESI) calcd for [$C_{35}H_{48}N_2O_5$+Na^+] 599.3455, found 599.3445.

(3*S*,6*R*,10*R*,16*S*)-3-Benzyl-10-(hydroxymethyl)-4,6-dimethyl-16-propyl-1-oxa-4,11-diazacyclohexa-decane-2,5,12-trione (1-*RS*). To a solution of (*S*)-(*S*)-8-(((*R*)-1-(benzyloxy)but-3-en-2-yl)-amino)-8-oxooctan-4-yl 2-((*R*)-*N*,2-dimethylpent-4-enamido)-3-phenylpropanoate (300 mg, 0.52 mmol) in 150 mL toluene was added Grubbs II catalyst (66 mg, 0.08 mmol) and the reaction mixture was refluxed for 20 h. The solvent was evaporated and the residue was filtered through silica gel (hexane/EtOAc 2:3) to yield 180 mg (63%) of crude (3*S*,6*R*,10*R*,16*S*)-3-benzyl-10-((benzyloxy)methyl)-4,6-di-

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methyl-16-propyl-1-oxa-4,11-diazacyclohexadec-8-ene-2,5,12-trione as a brown resin. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32−7.06 (m, 10H), 5.88−5.27 (m, 2H), 5.02−4.38 (m, 3H), 4.28−3.74 (m, 2H), 3.62−3.28 (m, 4H), 2.94−2.44 (m, 3H), 2.43−2.01 (m, 3H), 1.98−1.15 (m, 11H), 1.14−0.76 (m, 6H). HRMS (ESI) calcd for $[C_{33}H_{44}N_2O_5 + H^+]$ 549.3323, found 549.3319.

A solution of the above material (100 mg, 0.18 mmol) in 15 mL MeOH was hydrogenated over Pd−C (39 mg, 0.04 mmol) at 3 bar for 8 h. The catalyst was then removed by filtration and the solvent was evaporated. FC (DCM/acetone 7:3 + 3% MeOH) on silica gel 60 (20−45 μm) gave 18.3 mg (22%) of **1-*RS*** (purity 94%), and 37.5 mg (45%) of a 1:1 mixture of **1-*RS*** and (the putative) 14*S*-**1-*RS*** and 7.5 mg (9%) of 14*S*-**1-*RS*** as amorphous white solids. **1-*RS***: $[\alpha]_D^{24}$ = −89.9° (*c* 0.52, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34−7.10 (m, 5H), 6.14 (d, *J* = 6.2 Hz, 1H), 5.08−5.00 (m, 1H), 5.04 (br s, 1H), 3.87−3.78 (m, 1H), 3.70−3.62 (m, 2H), 3.55 (dd, *J* = 11.2, 6.6 Hz, 1H), 3.47 (dd, *J* = 13.7, 10.8 Hz, 1H), 3.27 (dd, *J* = 13.7, 4.9 Hz, 1H), 2.68 (s, 3H), 2.65−2.47 (m, 2H), 2.15−2.06 (m, 1H), 1.91−1.74 (m, 4H), 1.70−1.17 (m, 11H), 1.05 (d, *J* = 6.9 Hz, 3H), 0.93 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): 176.0, 175.3, 171.1, 138.4, 129.3, 128.5, 126.6, 73.7, 67.4, 67.1, 51.8, 39.3, 37.0, 36.1, 35.5, 34.6, 34.2, 32.3, 29.2, 22.3, 21.9, 18.9, 18.1, 13.9. (Single isomer). IR: ν 3308, 2935, 2867, 1722, 1638, 1538, 1455, 1243, 1067, 752 cm^{-1}. HRMS (ESI) calcd for $[C_{26}H_{40}N_2O_5 + H^+]$ 461.3010, found 461.3012.

(*S*)-(*R*)-8-(((*R*)-1-(Benzyloxy)But-3-en-2-yl)amino)-8-oxooctan-4-yl-2-((*R*)-*N*,2-dimethylpent-4-enamido)-3-phenylpropanoate. To a solution of ***ent*-6** (70 mg, 0.61 mmol) and HATU (240 mg, 0.63 mmol) in 3.7 mL dry DMF was added DIEA (0.2 mL, 1.15 mmol) and the mixture was stirred for 5 min at rt. Then (*S*)-(*R*)-8-(((*R*)-1-(benzyloxy)but-3-en-2-yl)amino)-8-oxooctan-4-yl-2-(methylamino)-3-phenyl-propanoate (198 mg, 0.41 mmol) was added and the resulting solution was stirred at rt for 4.5 h. After removal of DMF 7.5 mL DCM and 7.5 mL 10% MeCN in water were added and the phases were separated. The aq. solution was extracted twice with 7.5 mL DCM, the combined organic extracts were dried over $MgSO_4$, and the solvent was evaporated. FC (hexane/EtOAc 1:1 + 2% Et_3N) gave 156 mg (66%) of (*S*)-(*R*)-8-(((*R*)-1-(benzyloxy)but-3-en-2-yl)amino)-8-oxooctan-4-yl-2-((*R*)-*N*,2-dimethylpent-4-enamido)-3-phenylpropanoate as yellowish resin. $[\alpha]_D^{24}$ = −27.9° (*c* 0.36, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38−7.14 (m, 10H), 6.14 (d, *J* = 8.0 Hz, 1H), 5.93−5.82 (m, 1H), 5.46−5.33 (m, 2H), 5.28−5.15 (m, 2H), 5.05−4.79 (m, 3H), 4.74−4.63 (m, 1H), 4.58−4.48 (m, 2H), 3.59−3.52 (m, 2H), 3.38 (dd, *J* = 14.7, 5.4 Hz, 1H), 3.07−2.79 (m, 2H), 2.88 (*s*, 3H), 2.65−2.55 (m, 1H), 2.30−2.11 (m, 2H), 1.95−1.84 (m, 1H), 1.73−1.42 (m, 6H), 1.37−1.19 (m, 2H), 1.05 (d, *J* = 6.7 Hz, 3H), 0.89 (d, *J* = 7.3 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 176.5, 172.1, 172.1, 137.9, 137.0, 136.0, 135.9, 135.86, 128.8, 128.4, 127.7, 116.5, 116.4, 116.1, 116.0, 74.8, 74.7, 73.3, 73.20, 73.17, 71.8, 71.7, 58.1, 51.0, 50.92, 50.89, 37.9, 36.18, 36.10, 35.15, 35.8, 34.7, 33.3, 21.43, 21.36, 18.5, 16.9, 13.94, 13.86. IR: ν 3312, 3065, 3031, 2959, 2932, 2871, 1732, 1627, 1092 cm^{-1}. HRMS (ESI) calcd for $[C_{35}H_{48}N_2O_5 + Na^+]$ 599.3455, found 599.3455.

(3*S*,6*R*,10*R*,16*R*)-3-Benzyl-10-(hydroxymethyl)-4,6-dimethyl-16-propyl-1-oxa-4,11-diazacyclohexa-decane-2,5,12-trione (1-*RR*). To a solution of (*S*)-(*R*)-8-(((*R*)-1-(benzyloxy)but-3-en-2-yl)amino)-8-oxooctan-4-yl 2-((*R*)-*N*,2-dimethylpent-4-enamido)-3-phenylpropanoate (98.2 mg, 0.17 mmol) in 50 mL toluene was added Grubbs II catalyst (23.4 mg, 0.03 mmol) and the reaction mixture was refluxed for 16 h. The solvent was then evaporated and the residue was purified by FC (hexane/EtOAc 1:2) to afford 83 mg (89%) of crude (3*S*,6*R*,10*R*,16*R*)-3-benzyl-10-((benzyloxy)methyl)-4,6-dimethyl-16-propyl-1-oxa-4,11-diazacyclohexadec-8-ene-2,5,12-trione as a brown resin. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42−7.08 (m, 10H), 6.14−5.28 (m, 2H), 5.02−4.38 (m, 3H), 4.28−4.01 (m, 1H), 3.88−3.15 (m, 3H), 3.07−2.48 (m, 4H), 2.47−1.89 (m, 5H), 1.86−1.21 (m, 10H), 1.11−0.71 (m, 6H). HRMS (ESI) calcd for $[C_{33}H_{43}N_2O_5 + H^+]$ 549.3323, found 549.3331.

A solution of the above material (83 mg, 0.15 mmol) in 15 mL MeOH was hydrogenated over Pd−C (3.2 mg, 0.003 mmol) at 3 bar 19 h. Additional Pd−C (27.5 mg, 0.026 mmol) was then added and hydrogenation was continued for 8 h (3 bar). A third portion of Pd−C (17.5 mg, 0.016 mmol) was added and hydrogenation was further continued for 15 h. The catalyst was removed by filtration and the solvent was evaporated. FC (DCM/acetone 7:3 + 3% MeOH) on silica gel 60 (20−45 μm) gave 31 mg (44%) of a 3:1 mixture of **1-*RR*** and (the putative) 14*S*-**1-*RR*** and 4 mg (6%) of 14*S*-**1-*RR*** as amorphous white solids. **1-*RR***: $[\alpha]_D^{24}$ = −57.0° (*c* 0.31, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26−7.06 (m, 5H), 6.62 (d, *J* = 8.0 Hz, 1H), 4.91−4.82 (m, 1H), 3.87−3.78 (m, 1H), 3.65−3.55 (m, 2H), 3.54−3.43 (m, 2H), 3.37−3.18 (m, 2H), 2.69 (s, 3H), 2.40−2.32 (m, 1H), 2.29−2.20 (m, 1H), 2.08−1.99 (m, 1H), 1.76−1.00 (m, 15H), 0.97 (d, *J* = 7.0 Hz, 3H), 0.82 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): 175.8, 174.4, 170.0, 138.3, 129.3, 128.4, 126.6, 74.9, 66.5, 66.4, 52.2, 39.4, 36.9, 36.8, 34.8, 34.0, 33.2, 31.2, 29.6, 25.1, 21.9, 18.9, 18.2, 14.0. IR: ν 3299, 2933, 2866, 1733, 1637, 1547, 1459, 1276, 1083, 752 cm^{-1}. HRMS (ESI) calcd for $[C_{26}H_{40}N_2O_5 + H^+]$ 461.3010, found 461.3011.

■ ASSOCIATED CONTENT

Supporting Information

HPLC data for **1**; HPLC data for FDAA derivatives of **9** and ***ent*-9**; ^{1}H and ^{13}C NMR spectra for intermediates and final products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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