

## Synthesis of modified miuraenamides – the Ugi approach

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Dedication to Prof. Horst Kunz on the occasion of his 80<sup>th</sup> birthday

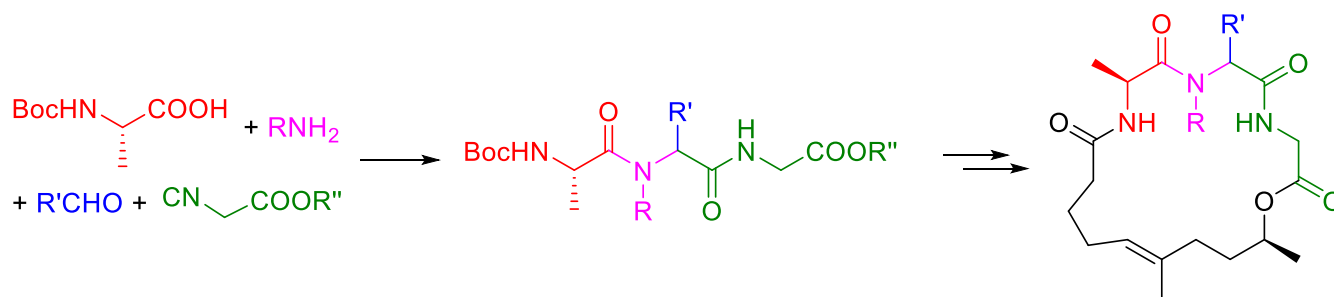
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### Abstract

Miuraenamides, a group of marine cyclodepsipeptides, closely related to jasplakinolide and geodiamolide are found to accelerate nucleation and polymerization of actin, and therefore interfere with cell division processes, at concentrations in the low nanomolar range. For SAR studies derivatives are synthesized via Ugi reaction, which provides the complete tripeptide fragment in only one step. While a wide range of modifications are possible at the C-terminus of the peptide, variations at the central position are not tolerated. Neither modifications in the polyketide.

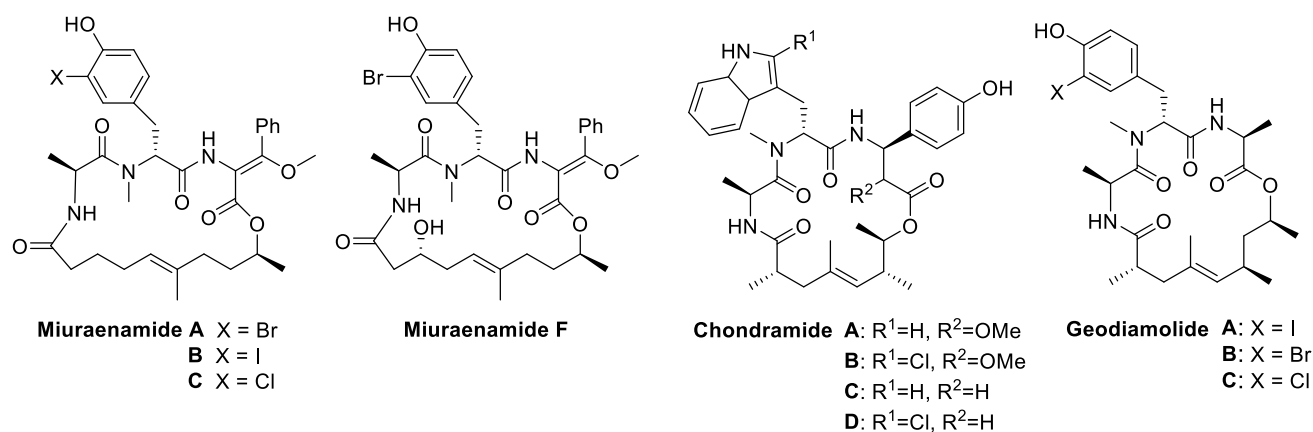


**Keywords:** Actin, cyclodepsipeptides, multicomponent reactions, natural products, polyketides, Ugi reactions

## Introduction

Myxobacteria, highly interesting Gram-negative  $\delta$ -proteobacteria, were initially considered as terrestrial microorganisms<sup>1,2</sup> but in the meanwhile a lot of marine representatives have been discovered during the last years.<sup>3,4</sup> Their rich secondary metabolism makes them one of the best natural product producers,<sup>5,6</sup> and many of their metabolites are interesting candidates for drug development.<sup>7</sup>

In 2006, Lizuka *et al.* isolated a novel lightly halophilic myxobacterium, *Paraliomyxa miuraensis*, from a soil sample at the coast of Japan.<sup>8</sup> Investigating the secondary metabolites produced by this species resulted in the isolation of miuraenamides A and B<sup>8</sup> and two years later also of the derivatives C-F (Figure 1).<sup>9</sup> The miuraenamides are structurally closely related to a range of other cyclodepsipeptides, such as the chondramides,<sup>10-12</sup> also produced by myxobacteria or the geodiamolides,<sup>13</sup> seragamides<sup>14</sup> or jasplakinolide.<sup>15,16</sup> All these natural products have been isolated from sponges, but probably they are not produced by them but might also be secondary metabolites from bacteria living in them.<sup>9</sup>



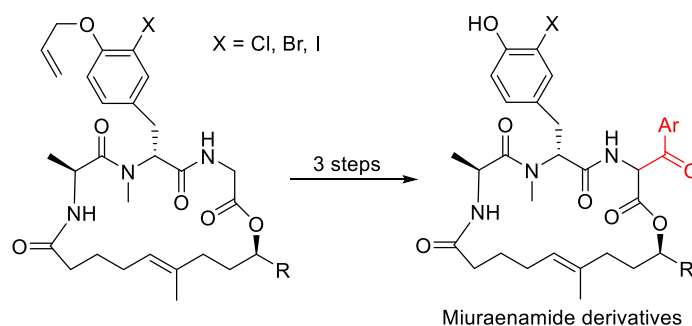
**Figure 1.** Natural occurring cyclodepsipeptides.

Like the other cyclodepsipeptides the miuraenamides can be divided into two major building blocks: a tripeptide containing a halogenated tyrosine in the central position and a polyketide fragment. The derivatives mainly differ in the halogenation pattern of the tyrosine and the C-terminal unusual amino acid containing a methoxyacrylate (*E* or *Z*) motif. In miuraenamide F an additional hydroxylated polyketide is incorporated. Differences in this hydroxycarboxylic acid are also found, e.g. in the chondramides or geodiamolides, not only in the position of the double bond and the substitution pattern, but also the chain length.

By far most investigations concerning the biological activity and the mode of action were carried out with jasplakinolide (jaspamide), which shows high cytotoxicity towards a range of leukemia, breast and prostate cancer cell lines.<sup>17</sup> Jasplakinolide was found to initiate actin polymerization and stabilizes already formed actin microfilaments, which causes significant morphological changes in the cell.<sup>18,19</sup> The same effects were also observed for the geodiamolides,<sup>17</sup> chondramides<sup>20,21</sup> and the miuraenamides.<sup>22-24</sup> While the other natural products contain six to seven stereogenic centres, the miuraenamides A-C contain only three asymmetric C-atoms (and one stereoisomeric double bond). Therefore, the miuraenamides might be ideal candidates for the development of potential anti-tumor drugs.

## Results and Discussion

Concerning our ongoing interest into the syntheses of biological active natural products<sup>25-30</sup> we also focused on the synthesis of chondramide derivatives<sup>31,32</sup> and we developed a straightforward protocol towards the miuraenamides<sup>33</sup> based on a late stage modification approach.<sup>34</sup> This concept allowed the synthesis of a small library of miuraenamide derivatives via aldol reaction at the C-terminal position of a glycine containing cyclo-depsipeptide (Scheme 1).<sup>35</sup> SAR studies clearly indicated that the C-terminal amino acid can be varied in a wide range without significant effect on the biological activity of the derivatives. Obviously the unusual unsaturated amino acid is not required for the anti-cancer activity, a derivative without a side chain was found to be even more active towards several cell lines than the natural products. Therefore, the already rather simple structure could even be further simplified, what forced us to investigate also modifications at the central amino acid and the polyketide fragment.



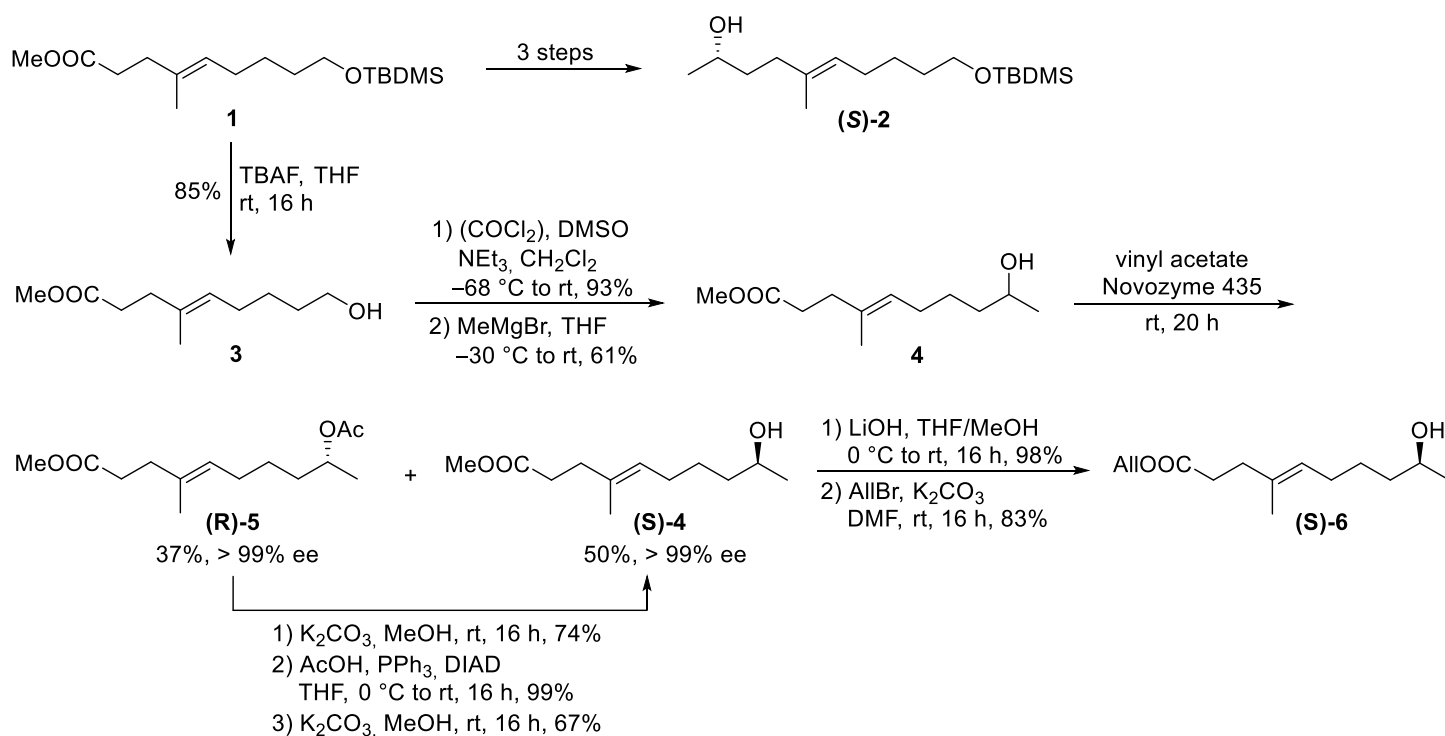
**Scheme 1.** Miuraenamides via late stage modifications.

In the miuraenamides the methyl-substituted double bond is at another position compared to all other cyclodepsipeptides (Figure 1). Therefore, we wanted to see what happens if we incorporate an “inverted” chondramide-type hydroxyacid with the same chain length. On the other hand, tripeptides with a N-methylated amino acid in the central position should be easily accessible via Ugi reaction,<sup>36,37</sup> a protocol used previously, e. g. for the synthesis of cyclic peptides.<sup>38-45</sup> Although, these reactions should give mixtures of diastereomers, this is not a serious issue in this case, because one might expect that the different diastereomers should be separable, at least in the cyclized form. And in principle, all stereoisomers can be interesting candidates for SAR studies.

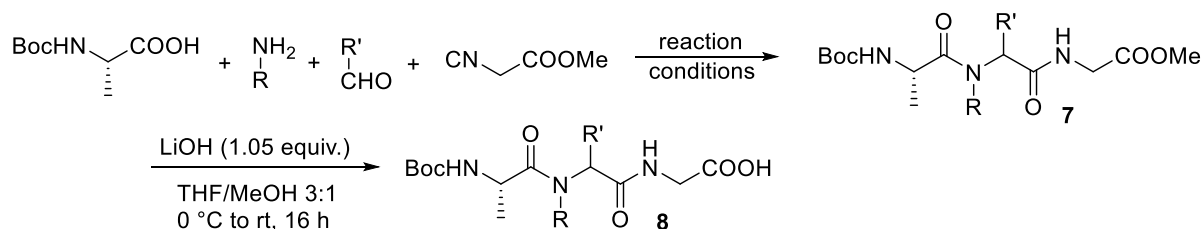
For the synthesis of the “inverted” polyketide fragment we started from the same building block **1**, which was previously used during the synthesis of the miuraenamides. In this case **1** was converted into **2**, which was coupled to the tripeptide and later on oxidized to the carboxylic acid which was subjected to cyclization (Scheme 2). Now, cleavage of the silyl protecting group, Swern oxidation and subsequent methyl Grignard addition gave rise to racemic secondary alcohol **4**, which was subjected to enzymatic kinetic resolution. Both, the (*S*)-alcohol as well as the (*R*)-acetate **5** were obtained as pure enantiomer. Because we were only interested in (*S*)-**4**, (*R*)-**5** was subjected to saponification, Mitsunobu reaction to (*S*)-**5** and a second saponification provided finally additional (*S*)-**4**. Finally the methyl ester was converted into the corresponding allyl ester (*S*)-**6** which could later on be cleaved without affecting the secondary ester.

The desired tripeptides **8** were obtained by Ugi reaction (Scheme 3). Besides phenylacetaldehyde (providing phenylalanine derivatives) also a range of aromatic aldehydes were used generating substituted aryl glycines (Table 1). Since arylglycines are known to be relatively sensitive to epimerization, we expected that the analogues cyclic depsipeptides might undergo “deracemization” towards the thermodynamically

most stable stereoisomer, at least in some cases and the presence of base. This approach does not only allow the synthesis of *N*-methylated central amino acids, but may be used also for all kind on *N*-substituents. Exemplarily also an allyl substituent was incorporated. Using allyl amine as one component provided the desired product in high yield, although the reaction took two days to go to completion (entry 1). To speed up the process we carried out the further Ugi reactions at higher temperature in the microwave ( $\mu$ W), and most reactions were finished in 30–90 min. In most cases the yields obtained were only moderate, especially in case of the phenylacetaldehydes (entry 6), but the whole peptide **7** was obtained in only one step. All products were formed as almost 1:1 diastereomeric mixtures. Some of the derivatives could be separated by flash chromatography but the question was if this makes sense, because the next step was the saponification of the terminal methyl ester. As expected, the free tripeptide acids **8** were formed as a 1:1 mixture, independent if the ester was used in enantiomeric pure form or as stereoisomeric mixture, a clear indication for the configurational lability of the aryl glycine. Therefore, later on all esters **7** were saponified as diastereomeric mixtures.



**Scheme 2.** Synthesis of polyketide fragment (**S**)-6.

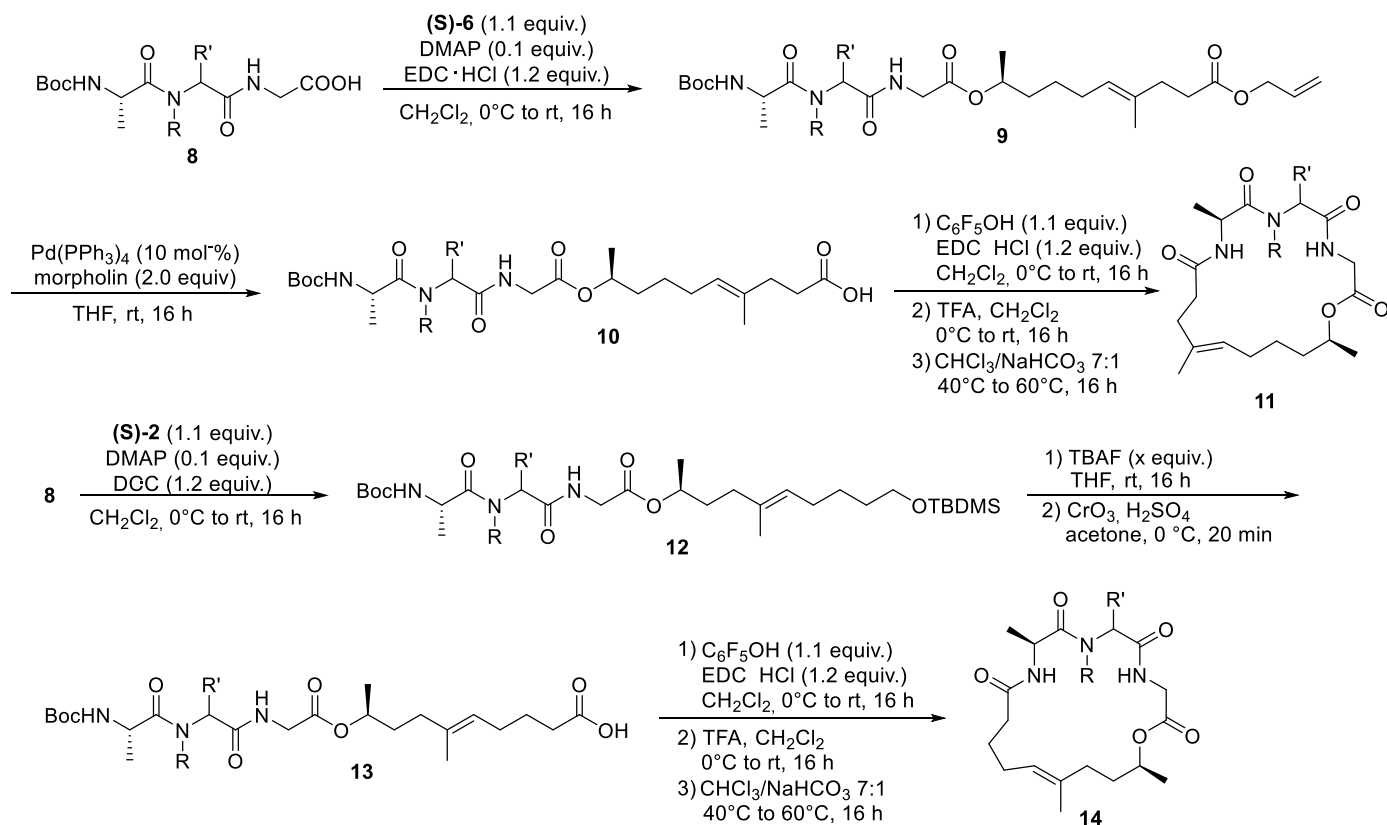


**Scheme 3.** Synthesis of tripeptides via Ugi reaction.

**Table 1.** Synthesis of tripeptides **8** via Ugi reaction/saponification

Entry	R	R'	reaction conditions	<b>7</b>	Yield (%)	<b>8</b>	Yield (%)
1	Allyl	Ph	EtOH, 0 °C to rt, 2d	<b>7a</b>	84	<b>8a</b>	90
2	Me	Ph	EtOH, $\mu$ W, 150W, 80 °C, 30 min	<b>7b</b>	66	<b>8b</b>	84
3	Me	3-Br-4-allyloxy-C <sub>6</sub> H <sub>3</sub>	CF <sub>3</sub> CH <sub>2</sub> OH, $\mu$ W, 150W, 100 °C, 75 min	<b>7c</b>	52	<b>8c</b>	93
4	Me	3-Cl-4-allyloxy-C <sub>6</sub> H <sub>3</sub>	CF <sub>3</sub> CH <sub>2</sub> OH, $\mu$ W, 150W, 100 °C, 90 min	<b>7d</b>	28	<b>8d</b>	77
5	Me	2-naph	CHCl <sub>3</sub> , $\mu$ W, 150W, 80 °C, 30 min	<b>7e</b>	36	<b>8e</b>	>99
6	Me	Bn	C <sub>2</sub> H <sub>4</sub> Cl <sub>2</sub> , $\mu$ W, 150W, 100 °C, 120 min	<b>7f</b>	33	<b>8f</b>	65

The tripeptide acids **8** were subsequently coupled with polyketide (**S**)-**6** to **9** using the Steglich protocol (Scheme 4, Table 2).<sup>46</sup> To be able to compare the new miuraenamides with the inverted polyketide directly with the natural products, we also coupled (**S**)-**6** with the original tripeptide containing 4-allyloxy-3-bromotyrosine (**8g**). After cleavage of the allyl ester **10** with Pd(PPh<sub>3</sub>)<sub>4</sub>/morpholine the free acid **11** was activated as pentafluorophenyl ester according to Schmidt et. al.<sup>47,48</sup> The Boc-protecting group was removed with trifluoroacetic acid and the salt solution was added dropwise to a vigorously stirred suspension of CHCl<sub>3</sub> and sat. NaHCO<sub>3</sub> solution. Stirring overnight gave rise to the desired macrocyclic products **11**. An indeed, our expectations became fulfilled, at least in part.

**Scheme 4.** Synthesis of miuraenamide derivatives **11** and **14**.

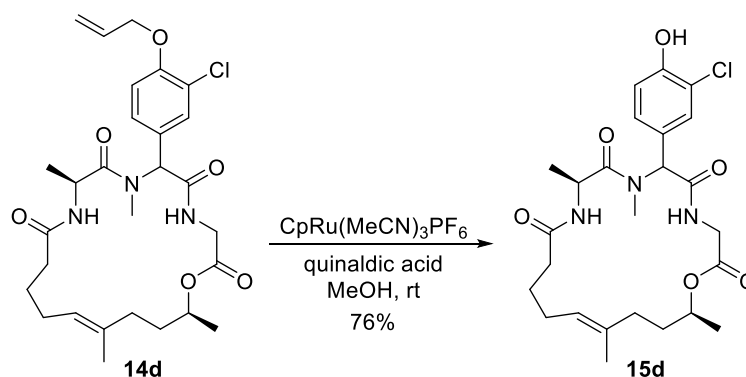
**Table 2.** Synthesis of miuraenamamide derivatives **11** and **15**

Entry	2/6	8	R	R'	9/12	Yield (%)	10/13	Yield (%)	11/14	d.r.	Yield (%)
1	(S)-6	8a	Allyl	Ph	9a	63	10a	60	11a	1:1	41
2	(S)-6	8b	Me	Ph	9b	67	10b	52	11b	9:1	44
3	(S)-6	8c	Me	3-Br-4-allyloxy-C <sub>6</sub> H <sub>3</sub>	9c	60	10c <sup>(a)</sup>	83	11c	--	--
4	(S)-6	8d	Me	3-Cl-4-allyloxy-C <sub>6</sub> H <sub>3</sub>	9d	60	10d <sup>(a)</sup>	98	11d <sup>(a)</sup>	7:3	38
5	(S)-6	8e	Me	2-naphth	9e	59	10e	98	11e	1:1	13
6	(S)-6	8f	Me	Bn	9f	60	10f	98	11f	1:1	27+26 <sup>(b)</sup>
7	(S)-6	8g	Me	(R)-3-Br-4-allyloxy-C <sub>6</sub> H <sub>3</sub> CH <sub>2</sub>	9g	49	10g <sup>(a)</sup>	98	11g <sup>(a)</sup>	>99:1	9
8	(S)-2	8d	Me	3-Cl-4-allyloxy-C <sub>6</sub> H <sub>3</sub>	12d	47	13d	46	14d	66:34	71
9	(S)-2	8e	Me	2-naphth	12e	74	13e	68	14e	78:22	46

(a) without an phenolic allyl protecting group. (b) Yields of the separated diastereomers.

While during the whole sequence the diastereomeric ratios of the tripeptides **7** and **8** were in all cases around 1:1, **11b** was obtained as a 9:1 diastereomeric mixture. Surprisingly the ratio for the corresponding *N*-allyl derivative **11a** was unchanged. Obviously, in case of **11b** an equilibration occurred either during cyclization or afterwards. This effect was also observed with several other derivatives, although not in such a high ratio. In case of the halogenated allyl ethers **10c**, **10d** and **10g**, both allyl protecting groups were removed simultaneously, and probably the free phenolic group caused problems in the cyclization step, especially for the bromo derivatives. In case of **10g** the yield of the macrocycle was rather low, and the reaction of **10c** resulted in complete decomposition of the substrate, while the corresponding chloro derivative **10d** caused no significant problems.

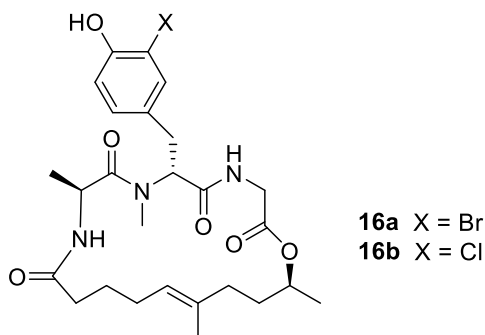
Exemplarily, some of the tripeptides **8** were also coupled with the original polyketide precursor (**S**)-**2** to figure out the influence of the side chain on the activity. Besides an unpolar naphthyl sidechain, also a protected chlorophenol was incorporated, which should be close to the natural substituent in miuraenamamide C, missing only the benzylic carbon. In this case the allyl-protected phenol was subjected to cyclization, which occurred in excellent 71%, a further indication, that the free OH-group might be the critical functionality. Finally, the phenolic allyl protecting group of **14d** was cleaved using CpRu(MeCN)<sub>3</sub>PF<sub>6</sub> as a catalyst (Scheme 5).<sup>49</sup>

**Scheme 5.** Deprotected of allyl-protected cyclopeptide **14d**.

The cytotoxicity of all new cyclic miuraenamides derivatives was investigated using two human cancer cell lines, HCT-116 (colon cancer) and U-2 OS (osteosarcoma). Some representative results are summarized in Table 3. For comparison, also the data for the simplified, highly active derivatives **16a/b** (Figure 2, entries 6 and 7) are shown. Interestingly, all new derivatives showed a comparable cytotoxicity in the mid  $\mu\text{M}$  range, far away from the activity of the simplified miuraenamides **16**. Although the bromo derivative **16a** is significantly more active than the chloro analogue **16b**, even this compound is around 1000-fold more active than the best new derivative (entry 1). Obviously modification at the central position of the tripeptide as well as in the polyketide fragment are not tolerated, independent if polar or unpolar groups are introduced. Even derivative **11g** with the correct tripeptide was as inactive as all the others. Even if the same substitution pattern is used as in the miuraenamides, removal of the benzylic  $\text{CH}_2$ -groups is also not accepted (entry 6 vs. 8).

**Table 3.** Cytotoxicity of miuraenamides **11** and **14–16**

Derivatives with “inverted” polyketide			
Entry	Derivative	HCT-116 $\text{IC}_{50}$ ( $\mu\text{M}$ )	U-2 OS $\text{IC}_{50}$ ( $\mu\text{M}$ )
1	<b>11e</b>	29.4	34.7
2	<b>11f</b>	76.8	85.0
3	<b>11g</b>	46.4	66.9
Derivatives with “original” polyketide			
Entry	Derivative	HCT-116 $\text{IC}_{50}$ ( $\mu\text{M}$ )	U-2 OS $\text{IC}_{50}$ ( $\mu\text{M}$ )
4	<b>14d</b>	50.3	10.0
5	<b>14e</b>	64.1	44.0
6	<b>15d</b>	81.1	73.2
7	<b>16a</b>	0.0012	0.0048
8	<b>16b</b>	0.023	0.073



**Figure 2.** Highly cytostatic simplified miuraenamide derivatives.

## Conclusions

In conclusion, we could show that Ugi reactions provide easily tripeptides which can directly be incorporated into new miuraenamide derivatives. Although the yields are moderate in certain cases, application of

microwave heating speeds up the reaction significantly providing acceptable yields. Detailed SAR studies indicate that modifications at the C-terminus are well accepted, but not at the central position. Replacing the hydroxy acid by a geodiamolide- or chondramide-type polyketide fragment (inverted polyketide) is also not tolerated. All new derivatives synthesized showed comparable cytotoxicity in the mid  $\mu\text{M}$  range, which is at least 1000-fold lower than comparable simplified miuraenamides derivatives. Further investigations, especially regarding the binding mode, are in progress.

## Experimental Section

**General.** All air- or moisture-sensitive reactions were carried out in dried glassware ( $>100\text{ }^\circ\text{C}$ ) under an atmosphere of nitrogen. Dried solvents were distilled before use: Dichloromethane was purchased from Sigma-Aldrich. The products were purified by flash chromatography on silica gel (0.063–0.2 mm). Mixtures of EtOAc and petroleum ether were generally used as eluents. Analytical TLC was performed on pre-coated silica gel plates (Macherey-Nagel, Polygram<sup>®</sup> SIL G/UV254). Visualization was accomplished with UV-light and  $\text{KMnO}_4$  or Ninhydrin solution. Melting points were determined with a *Laboratory Devices MEL-TEMP II* melting point apparatus and are uncorrected.  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded with *Bruker AV II 400* [400 MHz ( $^1\text{H}$ ) and 100 MHz ( $^{13}\text{C}$ )] and *Bruker DRX and AV 500* [500 MHz ( $^1\text{H}$ ) and 125 MHz ( $^{13}\text{C}$ )] spectrometers in  $\text{CDCl}_3$ , unless otherwise specified. Chemical shifts are reported in ppm relative to TMS, and  $\text{CHCl}_3$  was used as the internal standard. Melting points were determined with a MEL-TEMP II (Laboratory Devices) melting point apparatus and are uncorrected.  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded with *Bruker AV II 400* [400 MHz ( $^1\text{H}$ ) and 100 MHz ( $^{13}\text{C}$ )] and *Bruker DRX and AV 500* [500 MHz ( $^1\text{H}$ ) and 125 MHz ( $^{13}\text{C}$ )] spectrometers in  $\text{CDCl}_3$ , unless otherwise specified. Chemical shifts are reported in ppm relative to TMS, and  $\text{CHCl}_3$  was used as the internal standard. Mass spectra were recorded with a Finnigan MAT 95 spectrometer (quadrupole) using the CI technique.

**(4E)-9-Hydroxy-4-methyl-4-nonenoic acid methyl ester (3).** Silylether **1** (1.02 g, 3.24 mmol) was dissolved in THF (6.5 mL) before TBAF $\cdot$ 3H $_2$ O (1.23 g, 3.89 mmol) in THF (7 mL) was added. After stirring overnight the solution was diluted with ethyl acetate (20 mL) and was washed with 1N HCl solution, brine and dried ( $\text{Na}_2\text{SO}_4$ ). After evaporation of the solvent *in vacuo* and flash chromatography (silica, hexanes:ethyl acetate 1:1) alcohol **3** (550 mg, 2.75 mmol, 85%) was obtained as colorless oil.  $R_f$  (**3**) = 0.36 (silica, hexanes:ethyl acetate 1:1).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 1.40 (m, 2 H), 1.55 (m, 2 H), 1.61 (s, 3 H), 2.01 (td,  $J$  7.3, 7.3 Hz, 2 H), 2.31 (t,  $J$  7.2 Hz, 2 H), 2.42 (m, 2 H), 3.64 (t,  $J$  6.8 Hz, 2 H), 3.67 (s, 3 H), 5.17 (tq,  $J$  7.3 Hz, 1.3 Hz, 1 H) ppm.  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 15.9 (q), 25.8 (t), 27.5 (t), 32.3 (t), 33.0 (t), 34.7 (t), 51.5 (q), 62.9 (t), 125.2 (d), 133.6 (s), 173.9 (s) ppm. HRMS (CI) calc. for  $\text{C}_{11}\text{H}_{21}\text{O}_3^+$  [ $\text{M}+\text{H}$ ] $^+$ : 201.1485, found 201.1469.

**(4E)-9-Hydroxy-4-methyl-4-decenoic acid methyl ester (rac-4).** Oxalyl chloride (3.63 mL, 43.2 mmol) in dichloromethane (70 mL) was cooled to  $-68\text{ }^\circ\text{C}$  before DMSO (6.14 mL, 86.4 mmol) in dichloromethane (15 mL) was added in such a rate that a temperature of  $-68\text{ }^\circ\text{C}$  was not passed over. 5 Minutes after complete addition the alcohol **3** was added in dichloromethane (22 mL) and stirring was continued for further 30 min.  $\text{NEt}_3$  (20 mL, 144 mmol) was added and the mixture was allowed to warm to room temperature overnight. The solution was hydrolyzed and the aqueous layer was extracted three times with dichloromethane and ethyl acetate (20 mL each). The organic layer was dried ( $\text{Na}_2\text{SO}_4$ ) and after evaporation of the solvent *in vacuo* and flash chromatography (silica, hexanes:ethyl acetate 7:3) the corresponding aldehyde (5.33 g, 26.9 mmol, 93%) was obtained as pale yellow oil and directly used in the subsequent Grignard reaction.



The aldehyde (890 mg, 4.06 mmol) was dissolved in THF (16 mL) and cooled to  $-30\text{ }^{\circ}\text{C}$  before MeMgBr (4.9 mL, 4.90 mmol, 1M in  $\text{Bu}_2\text{O}$ ) was added dropwise. Stirring was continued for further 30 min before the reaction mixture was warmed up to room temperature and hydrolyzed with 1M  $\text{NH}_4\text{Cl}$  (20 mL). The aqueous layer was extracted trice with ether (15 mL) and the combined organic layers were dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated *in vacuo*. Flash chromatography (silica, hexanes:ethyl acetate 6:4) provided racemic alcohol **4** (530 mg, 2.48 mmol, 61% d. Th.) as colorless oil.  $R_f$  (**4**) = 0.28 (hexanes:ethyl acetate 6:4). HPLC (Chiracel OD-H, hexane/*i*-propanol 95:5,  $10\text{ }^{\circ}\text{C}$ , 1 mL/min, 210 nm):  $t_R$  [(**S**)-**4**] = 10.15 min,  $t_R$  [(**R**)-**4**] = 11.31 min.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 1.19 (d,  $J$  6.0 Hz, 3 H), 1.39–1.47 (m, 4 H), 1.61 (s, 3 H), 2.00 (td,  $J$  6.5, 6.5 Hz, 2 H), 2.31 (t,  $J$  8.0 Hz, 2 H), 2.42 (m, 2 H), 3.67 (s, 3 H), 3.79 (m, 1 H), 5.16 (td,  $J$  7.2, 0.8 Hz, 1 H) ppm.  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 15.9 (q), 23.5 (q), 25.8 (t), 27.7 (t), 33.0 (t), 34.7 (t), 38.8 (t), 51.5 (q), 68.1 (d), 125.2 (d), 133.5 (s), 173.9 (s) ppm. HRMS (CI) calc. for  $\text{C}_{12}\text{H}_{23}\text{O}_3^+$  [M+H] $^+$ : 215.1642, found 215.1640.

**(9S,4E)-9-Hydroxy-4-methyl-4-decenoic acid methyl ester [(S)-4]**. Racemic alcohol *rac*-**4** (2.84 g, 13.3 mmol) was dissolved in vinyl acetate (6.1 mL, 66.5 mmol) before Novozym 435 (28 mg) was added. The solution was shaken at room temperature and the reaction was monitored by HPLC. After 20 h the solution was filtered and the Novozym was washed with ether. After evaporation of the solvent *in vacuo*, flash chromatography (silica, hexanes:ethyl acetate 9:1, 6:4) provided (**S**)-**4** (1.43 g, 6.65 mmol, 50%, >99.9% *ee*) as colorless oil.  $R_f$  [(**S**)-**4**] = 0.19 (hexanes:ethyl acetate 9:1).  $[\alpha]_D^{20} = +6.0$  ( $c = 1.0$ ,  $\text{CHCl}_3$ ). NMR and analytical data are analogous to *rac*-**4**.

**(9R,4E)-9-Acetoxy-4-methyl-4-decenoic acid methyl ester [(R)-5]**. Acetate (**R**)-**5** (1.26 g, 4.91 mmol, 37% d. Th., >99% *ee*) was obtained as second product in the enzymatic kinetic resolution of *rac*-**4** as colorless oil.  $R_f$  [(**R**)-**5**] = 0.42 (hexanes:ethyl acetate 9:1).  $[\alpha]_D^{20} = +4.3$  ( $c = 1.0$ ,  $\text{CHCl}_3$ ). GC (Chirasil-Dex-CB:  $T_0$  (3 min) =  $80\text{ }^{\circ}\text{C}$ ,  $2\text{ }^{\circ}\text{C}/\text{min}$  to  $T = 200\text{ }^{\circ}\text{C}$  (3 min), injektor:  $T = 250\text{ }^{\circ}\text{C}$ , detektor:  $T = 275\text{ }^{\circ}\text{C}$ ):  $t_R$  [(**S**)-**5**] = 23.13 min,  $t_R$  [(**R**)-**5**] = 23.39 min.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 1.20 (d,  $J$  6.4 Hz, 3 H), 1.35 (m, 2 H), 1.47 (m, 2 H), 1.60 (s, 3 H), 1.98 (dt,  $J$  7.2, 7.2 Hz, 2 H), 2.03 (s, 3 H), 2.30 (t,  $J$  8.0 Hz, 2 H), 2.42 (m, 2 H), 3.67 (s, 3 H), 4.88 (m, 1 H), 5.14 (td,  $J$  7.3, 1.2 Hz, 1 H) ppm.  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 15.9 (q), 20.0 (q), 21.4 (q), 25.5 (t), 27.6 (t), 33.0 (t), 34.6 (t), 35.5 (t), 51.5 (q), 70.9 (d), 125.0 (d), 133.7 (s), 170.8 (s), 173.9 (s) ppm. HRMS (CI) calc. for  $\text{C}_{14}\text{H}_{25}\text{O}_4^+$  [M+H] $^+$ : 257.1747, found 257.1751.

**(9S,4E)-9-Hydroxy-4-methyl-4-decenoic acid allyl ester [(S)-6]**. Methyl ester (**S**)-**4** (1.42 g, 6.65 mmol) was dissolved in THF (6.7 mL) and a 1M LiOH solution in THF (8.7 mL, 8.7 mmol) was added. The solution was stirred overnight at room temperature before it was diluted with ethyl acetate (20 mL). The organic layer was washed trice with water. The combined aqueous layers were acidified with 1M HCl and extracted trice with dichloromethane (15 mL each). The combined organic layers were dried ( $\text{Na}_2\text{SO}_4$ ) and the solvent was evaporated *in vacuo* providing the corresponding acid (1.13 g, 5.64 mmol, 85%). This acid was dissolved in DMF (12 mL) and reacted with  $\text{K}_2\text{CO}_3$  (530 mg, 6.29 mmol) and allyl bromide (740 mg, 8.58 mmol). The solution was stirred overnight at room temperature, diluted with ethyl acetate (20 mL) and washed trice with water and once with 1M  $\text{KHSO}_4$ . After drying the organic layer ( $\text{Na}_2\text{SO}_4$ ) and evaporation of the solvent *in vacuo* flash chromatography (silica, hexanes:ethyl acetate 6:4) provided allyl ester (**S**)-**6** (1.13 g, 4.72 mmol, 83%) as a pale yellow oil.  $R_f$  [(**S**)-**6**] = 0.34 (hexanes:ethyl acetate 6:4).  $[\alpha]_D^{20} = +5.6$  ( $c = 1.0$ ,  $\text{CHCl}_3$ ).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 1.19 (d,  $J$  6.2 Hz, 3 H), 1.38–1.48 (m, 4 H, 3-H), 1.62 (s, 3 H), 2.0 (td,  $J$  6.8, 6.8 Hz, 2 H), 2.32 (t,  $J$  8.0 Hz, 2 H), 2.45 (t,  $J$  7.8 Hz, 2 H), 3.80 (m, 1 H), 4.58 (dt,  $J$  5.5, 1.5 Hz, 2 H), 5.16 (td,  $J$  7.0, 1.0 Hz, 1 H), 5.24 (dd,  $J_1 = 10.5$ , 1.2 Hz, 1 H), 5.32 (dd,  $J$  17.1, 1.5 Hz, 1 H), 5.92 (ddt,  $J$  17.1, 10.5, 5.8 Hz, 1 H) ppm.  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 15.9 (q), 23.5 (q), 25.8 (t), 27.7 (t), 33.1 (t), 34.6 (t), 38.8 (t), 65.0 (t), 68.0 (d), 118.1 (t), 125.2 (d), 132.3 (d), 133.5 (s), 173.1 (s) ppm. HRMS (CI) calc. for  $\text{C}_{14}\text{H}_{25}\text{O}_3^+$  [M+H] $^+$ : 241.1798, found 241.1803.

***N*-tert-Butoxycarbonyl-(*S*)-alanyl-(*N*-allyl-phenylglycyl)-glycine methyl ester (**7a**).** Benzaldehyde (0.51 mL, 5.00 mmol), allylamine (0.38 mL, 5.00 mmol) and *N*-Boc-Ala-OH (950 mg, 5.00 mmol) were dissolved in ethanol (5 mL) before methyl isocynoacetate (0.45 mL, 5.00 mmol) was added at 0 °C. The clear solution was stirred for two days at room temperature before it was diluted with dichloromethane (30 mL). The organic phase was washed with sat. NaHCO<sub>3</sub> (20 mL) and 1M KHSO<sub>4</sub> (20 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated *in vacuo*. Flash chromatography (silica, hexanes:ethyl acetate 1:1) provided tripeptide **7a** (1.82 g, 4.20 mmol, 84%) as a 56:44 diastereomeric mixture. Colorless solid, mp 36–38 °C. R<sub>f</sub> (**7a**) = 0.17 (hexanes:ethyl acetate 1:1). Diastereomer 1: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz): δ = 1.29 (d, *J* 6.8 Hz, 3 H), 1.43 (s, 9 H), 3.76 (s, 3 H), 3.91–4.21 (m, 4 H), 4.43 (q, *J* 7.0, 1 H), 4.96 (d, *J* 10.8, 1 H), 5.02 (d, *J* 18.3, 1 H), 5.19 (bs, 1 H), 5.27 (m, 1 H), 6.17 (s, 1 H), 7.17 (bs, 1 H), 7.32–7.43 (m, 5 H) ppm. <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz): δ = 17.9 (q), 28.3 (3 q), 41.2 (t), 46.7 (d), 48.8 (t), 52.2 (q), 62.5 (d), 80.1 (s), 117.2 (t), 128.4 (d), 128.7 (d), 130.1 (d), 133.5 (s), 156.1 (s), 169.6 (s), 170.1 (s), 175.1 (s) ppm. Diastereomer 2: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz): δ = 1.35 (d, *J*<sub>2,1</sub> = 6.5, 3 H), 1.43 (s, 9 H), 3.74 (s, 3 H), 3.80–4.31 (m, 4 H), 4.61 (q, *J* 7.3, 1 H), 4.96 (d, *J* 10.8, 1 H), 5.02 (d, *J* 18.3, 1 H), 5.36 (d, *J* 8.3, 1 H), 5.59 (m, 1 H), 6.06 (s, 1 H), 6.35 (bs, 1 H), 7.32–7.43 (m, 5 H) ppm. <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz): δ = 19.1 (q), 28.3 (q), 41.3 (t), 46.9 (d), 48.7 (t), 52.3 (q), 62.0 (d), 79.5 (s), 117.1 (t), 128.4 (d), 128.8 (d), 129.5 (d), 134.2 (s), 156.1 (s), 169.5 (s), 169.9 (s), 174.8 (s) ppm. HRMS (CI) calc. for C<sub>22</sub>H<sub>32</sub>N<sub>3</sub>O<sub>6</sub><sup>+</sup> [M+H]<sup>+</sup>: 434.2286, found 434.2313.

***N*-tert-Butoxycarbonyl-(*S*)-alanyl-[*N*-methyl-2-naphthylglycyl]-glycine methyl ester (**7e**).** A solution of 2-naphthaldehyde (156 mg, 1.00 mmol) and methylamine (124 μL 1.00 mmol, 33% in EtOH) in chloroform (1.0 mL) were stirred for 15 min before *N*-Boc-Ala-OH (119 mg, 1.20 mmol) and methyl isocynoacetate (90.0 μL, 1.00 mmol) in chloroform (0.5 mL) were added at 0 °C. After stirring for further 30 min, the reaction mixture was heated in a microwave (30 min, 80 °C, 150 W). After cooling to room temperature, the solution was worked up according to **7a**. The two diastereomeric products (1:1) could be separated by flash chromatography (silica, hexanes:ethyl acetate 1:1). Yield: 164 mg (0.359 μmol, 36%) colorless oil. Diastereomer 1: R<sub>f</sub> (**7e-1**) = 0.17 (hexanes:ethyl acetate 1:1). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz): δ = 1.40 (d, 3 H), 1.45 (s, 9 H), 2.95 (s, 3 H), 3.76 (s, 3 H), 4.01 (dd, 1 H), 4.21 (dd, 1 H), 4.68 (dq, 1 H), 5.51 (d, 1 H), 6.40 (bs, 1 H), 6.53 (s, 1 H), 7.40 (d, 1 H), 7.49–7.55 (m, 2 H), 7.82–7.88 (m, 3 H), 7.94 (s, 1 H) ppm. <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz): δ = 18.7 (q), 28.3 (q), 32.2 (q), 41.3 (t), 46.8 (d), 52.4 (q), 60.8 (d), 79.6 (s), 126.6 (d), 126.6 (d), 126.7 (d), 127.6 (d), 128.2 (d), 128.8 (d), 129.0 (d), 131.4 (s), 133.1 (s), 133.2 (s), 169.5 (s), 169.9 (s), 171.1 (s), 174.1 (s) ppm. Diastereomer 2: R<sub>f</sub> (**7e-2**) = 0.12 (hexanes:ethyl acetate 1:1). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz): δ = 1.34 (d, 3 H), 1.45 (s, 9 H), 2.97 (s, 3 H), 3.78 (s, 3 H), 4.07 (dd, 1 H), 4.18 (dd, 1 H), 4.65 (dq, 1 H), 5.45 (bs, 1 H), 6.51 (s, 1 H), 6.85 (bs, 1 H), 7.38 (d, 1 H), 7.49–7.55 (m, 2 H), 7.82–7.88 (m, 3 H), 7.95 (s, 1 H) ppm. <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz): δ = 18.7 (q), 28.3 (q), 32.2 (q), 41.3 (t), 46.8 (d), 52.3 (q), 60.4 (d), 79.9 (s), 126.5 (d), 126.7 (d), 126.7 (d), 127.6 (d), 128.2 (d), 128.3 (d), 129.1 (d), 131.8 (s), 133.0 (s), 133.2 (s), 169.3 (s), 170.0 (s), 170.1 (s), 174.3 (s) ppm. HRMS (CI) calc. for C<sub>24</sub>H<sub>32</sub>N<sub>3</sub>O<sub>6</sub><sup>+</sup> [M+H]<sup>+</sup>: 458.2286, found 458.2288.

***N*-tert-Butoxycarbonyl-(*S*)-alanyl-(*N*-allyl-phenylglycyl)-glycine (**8a**).** Methyl ester **7a** (1.00 g, 2.31 mmol) was dissolved in THF/MeOH (3:1, 11.6 mL) and a solution LiOH (58.0 mg, 2.42 mmol) in H<sub>2</sub>O (4.6 mL) was added. The solution was stirred overnight at room temperature before it was diluted with ethyl acetate (20 mL). The organic layer was washed trice with water. The combined aqueous layers were acidified with 1M HCl and extracted trice with dichloromethane (15 mL each). The combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>) and the solvent was evaporated *in vacuo* providing **8a** (0.87 g, 2.08 mmol, 90%) as pale yellow foam and as a 1:1 diastereomeric mixture. Mp 60–64 °C. R<sub>f</sub> (**8a**) = 0.10 (hexanes:ethyl acetate 1:1). Diastereomer 1: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz): δ = 1.29 (d, *J* 6.8 Hz, 3 H), 1.43 (s, 9 H), 3.87–4.18 (m, 4 H), 4.47 (q, *J* 6.8 Hz, 1 H), 5.01 (d, *J* 10.0 Hz, 1 H), 5.08 (d, *J* 16.6 Hz, 1 H), 5.29–5.42 (m, 2 H), 6.02 (s, 1 H), 7.11 (bs, 1 H), 7.29–7.39 (m, 5 H) ppm. <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz): δ = 17.9 (q), 28.3 (q), 41.5 (t), 46.7 (d), 49.2 (t), 63.1 (d), 80.3 (s), 117.6 (t), 128.7

(d), 128.8 (d), 129.4 (d), 133.2 (s), 156.1 (s), 171.8 (s), 171.9 (s) ppm. Signals of the ester and amide CO groups could not be detected. Diastereomer 2:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  = 1.33 (d,  $J$  6.8 Hz, 3 H), 1.43 (s, 9 H), 3.87–4.18 (m, 4 H, 4-H), 4.62 (m, 1 H), 5.01 (d,  $J$  10.0 Hz, 1 H), 5.08 (d,  $J$  16.6 Hz, 1 H), 5.56–5.68 (m, 2 H), 6.10 (s, 1 H), 6.70 (bs, 1 H), 7.29–7.39 (m, 5 H) ppm.  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz):  $\delta$  = 18.8 (q), 28.3 (q), 41.6 (t), 46.9 (d), 48.9 (t), 62.1 (d), 80.3 (s), 117.6 (t), 128.7 (d), 128.8 (d), 129.9 (d), 134.0 (s), 156.1 (s), 171.8 (s), 171.9 (s) ppm. Signal of the secondary amide CO groups could not be detected. HRMS (CI) calc. for  $\text{C}_{21}\text{H}_{30}\text{N}_3\text{O}_6^+$   $[\text{M}+\text{H}]^+$ : 420.2129, found 420.2135.

***N*-tert-Butoxycarbonyl-(*S*)-alanyl-(*N*-allyl-phenylglycyl)-glycine (2*S*,6*E*)-10-(allyloxy-carbonyl)-7-methyl-dec-6-en-2-yl ester (9a).** Tripeptide **8a** (252 mg, 0.60 mmol) and alcohol (**S**)-**6** (159 mg, 0.66 mmol) were dissolved in dichloromethane (4.8 mL). After cooling to 0 °C DMAP (7.30 mg, 0.06 mmol) and EDC·HCl (138 mg, 0.72 mmol) in dichloromethane (1.8 mL) were added. The mixture was allowed to warm to room temperature overnight before the solvent was removed *in vacuo*. The residue was dissolved in ether (15 mL) and the solution washed with 1N  $\text{KHSO}_4$  and sat.  $\text{NaHCO}_3$ , dried ( $\text{Na}_2\text{SO}_4$ ) and the solvent was evaporated *in vacuo*. Flash chromatography (silica, hexanes:ethyl acetate 6:4) provided tripeptide ester **9a** (241 mg, 0.38 mmol, 63%) as a 1:1 diastereomeric mixture.  $R_f$  (**9a**) = 0.34 (hexanes:ethyl acetate 6:4). Diastereomer 1:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  = 1.23 (m, 3 H), 1.30 (d,  $J$  6.8 Hz, 3 H), 1.33 (m, 2 H), 1.44 (s, 9 H), 1.53 (m, 2 H), 1.60 (s, 3 H), 1.98 (m, 2 H), 2.31 (t,  $J$  8.0 Hz, 2 H), 2.44 (t,  $J$  8.3 Hz, 2 H), 3.80 (dd,  $J$  17.6, 4.5 Hz, 1 H), 4.03 (m, 2 H), 4.25 (dd,  $J$  18.1, 6.0 Hz, 1 H), 4.44 (m, 1 H), 4.59 (m, 2 H), 4.91–5.19 (m, 5 H), 5.23 (d,  $J$  10.3 Hz, 1 H), 5.32 (dd,  $J$  17.0, 0.8 Hz, 1 H), 5.91 (m, 1 H), 6.05 (s, 1 H), 7.04 (m, 1 H), 7.32–7.44 (m, 5 H) ppm.  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz):  $\delta$  = 15.9 (q), 18.1 (q), 19.9 (q), 25.3 (t), 27.5 (t), 28.3 (q), 33.1 (t), 34.6 (t), 35.3 (t), 41.7 (t), 46.7 (d), 48.9 (t), 62.7 (d), 65.0 (t), 72.6 (d), 80.1 (s), 117.3 (t), 118.1 (t), 124.8 (d), 128.7 (d), 128.8 (d), 129.7 (d), 129.7 (s), 132.3 (d), 133.8 (s), 156.0 (s), 169.4 (s), 170.8 (s), 173.0 (s) ppm. Diastereomer 2:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  = 1.23 (m, 3 H), 1.36 (d,  $J$  6.8 Hz, 3 H), 1.33 (m, 2 H), 1.44 (s, 9 H), 1.53 (m, 2 H), 1.60 (s, 3 H), 1.98 (m, 2 H), 2.31 (t,  $J$  8.0 Hz, 2 H), 2.44 (t,  $J$  8.3 Hz, 2 H), 3.80 (dd,  $J$  17.6, 4.5 Hz, 1 H), 4.03 (m, 2 H), 4.25 (dd,  $J$  18.1, 6.0 Hz, 1 H), 4.59 (m, 2 H), 4.61 (m, 1 H), 4.91–5.19 (m, 5 H), 5.23 (d,  $J$  10.3, 1 H), 5.32 (dd,  $J$  17.0, 0.8 Hz, 1 H), 5.91 (m, 1 H), 6.11 (s, 1 H), 7.04 (m, 1 H), 7.32–7.44 (m, 5 H) ppm.  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz):  $\delta$  = 15.9 (q), 18.1 (q), 19.9 (q), 25.4 (t), 27.6 (t), 28.3 (q), 33.1 (t), 34.6 (t), 35.4 (t), 41.6 (t), 46.7 (d), 48.9 (t), 62.7 (d), 65.0 (t), 72.4 (d), 80.1 (s), 117.3 (t), 118.1 (t), 124.9 (d), 128.7 (d), 128.8 (d), 129.7 (d), 129.7 (s), 132.3 (2 d, C-5), 133.8 (s), 156.0 (s), 169.4 (s), 170.8 (s), 173.0 (s) ppm. HRMS (CI) calc. for  $\text{C}_{35}\text{H}_{52}\text{N}_3\text{O}_8^+$   $[\text{M}+\text{H}]^+$ : 642.3749, found 642.3751.

***N*-tert-Butoxycarbonyl-(*S*)-alanyl-(*N*-allyl-phenylglycyl)-glycine (2*S*,6*E*)-10-carboxy-7-methyl-dec-6-en-2-yl ester (10a).** Allylester **9a** (205 mg, 0.32 mmol) was dissolved in THF (6.4 mL) under  $\text{N}_2$ , before  $\text{Pd}(\text{PPh}_3)_4$  (37.0 mg, 0.032 mmol) and morpholine (55.4  $\mu\text{L}$ , 0.64 mmol) were added. The solution was stirred overnight at room temperature, before it was diluted with ethyl acetate (20 mL). The solution was washed with  $\text{H}_2\text{O}$  and brine (20 mL each), dried ( $\text{Na}_2\text{SO}_4$ ) and the solvent was evaporated *in vacuo* providing **10a** (115 mg, 0.19 mmol, 60%) as a pale yellow resin. Diastereomeric ratio: 1:1.  $R_f$  (**10a**) = 0.21 (hexanes:ethyl acetate 1:1). Diastereomer 1:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  = 1.21 (m, 3 H), 1.35 (d,  $J$  6.8 Hz, 3 H), 1.33 (m, 2 H), 1.44 (s, 9 H), 1.53 (m, 2 H), 1.61 (s, 3 H), 1.98 (td,  $J$  6.8, 6.8 Hz, 2 H), 2.31 (t,  $J$  6.8 Hz, 2 H), 2.45 (t,  $J$  7.0 Hz, 2 H), 3.80–4.11 (m, 4 H), 4.47 (qd,  $J$  6.8, 6.8 Hz, 1 H), 4.94–5.09 (m, 4 H), 5.16 (tq,  $J$  6.3, 0.8 Hz, 1 H), 5.62 (m, 1 H), 6.13 (s, 1 H), 7.18 (dd,  $J$  5.3, 5.3 Hz, 1 H), 7.30–7.43 (m, 5 H) ppm.  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz):  $\delta$  = 15.9 (q), 17.8 (q), 19.8 (q), 25.1 (t), 27.1 (t), 28.3 (q), 33.5 (t), 34.5 (t), 34.7 (t), 41.8 (t), 46.8 (d), 48.8 (t), 62.8 (d), 72.5 (d), 81.3 (s), 117.5 (t), 125.2 (d), 128.5 (d), 128.7 (d), 128.8 (d), 129.6 (s), 130.0 (d), 133.6 (s), 156.6 (s), 169.2 (s), 169.6 (s), 173.6 (s), 174.6 (s) ppm. Diastereomer 2:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  = 1.21 (m, 3 H), 1.30 (d,  $J$  6.5 Hz, 3 H), 1.33 (m, 2 H), 1.43 (s, 9 H), 1.53 (m, 2 H), 1.61 (s, 3 H), 1.98 (td,  $J$  6.8, 6.8 Hz, 2 H), 2.31 (t,  $J$  6.8 Hz, 2 H), 2.45 (t,  $J$  7.0 Hz, 2 H), 3.80–4.11 (m, 4 H, 4-H), 4.61 (qd,  $J$  7.3, 7.3 Hz, 1 H), 4.94–5.09 (m, 4 H), 5.16 (tq,  $J$  6.3, 0.8 Hz, 1 H), 5.49

(d,  $J$  8.5 Hz, 1 H), 6.10 (s, 1 H), 6.68 (dd,  $J$  5.3, 5.3 Hz, 1 H), 7.30–7.43 (m, 5 H) ppm.  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz):  $\delta$  = 16.0 (q), 17.8 (q), 19.6 (q), 25.1 (t), 27.1 (t), 28.3 (q), 33.5 (t), 34.5 (t), 34.7 (t), 41.8 (t), 46.8 (d), 48.8 (t), 62.8 (d), 72.4 (d), 81.3 (s), 117.5 (t), 125.2 (d), 128.5 (d), 128.7 (d), 128.9 (d), 129.6 (s), 130.0 (d), 133.6 (s), 156.6 (s), 169.2 (s), 169.6 (s), 173.6 (s), 174.6 (s) ppm. HRMS (CI) calc. for  $\text{C}_{37}\text{H}_{48}\text{N}_3\text{O}_8^+$   $[\text{M}+\text{H}]^+$ : 602.3436, found 602.3472.

**(9S,19S,14E)-6-Phenyl-7-allyl-9,14,19-trimethyl-1-oxa-4,7,10-triazacyclononadec-14-en-2,5,8,11-tetraon**

**(11a).** Acid **10a** (109.4 mg, 0.18 mmol) and pentafluorophenol (36.8 mg, 0.20 mmol) were dissolved in dichloromethane (1.8 mL) and the solution was cooled to 0 °C before EDC·HCl (38.3 mg, 0.20 mmol) was added. The reaction mixture was warmed to room temperature overnight, diluted with ethyl acetate (20 mL) and washed with sat.  $\text{NaHCO}_3$ . After drying ( $\text{Na}_2\text{SO}_4$ ) and evaporation of the solvent the crude active ester was dissolved in dichloromethane/trifluoroacetic acid 4:1 (2 mL) and the reaction was monitored by TLC. After Boc cleavage was complete, the solution was diluted with dichloromethane (2.7 mL) and was added dropwise to a suspension (80 mL) of chloroform/sat.  $\text{NaHCO}_3$  (7:1) at 40 °C. The solution was warmed up to 60 °C overnight, before it was diluted with  $\text{H}_2\text{O}$  (50 mL). The phases were separated and the aqueous layer was washed three times with dichloromethane. The combined organic layers were dried ( $\text{Na}_2\text{SO}_4$ ) and the solvent was evaporated *in vacuo*. The crude product was purified by flash chromatography (silica, hexanes:ethyl acetate 3:7) to give miuraenamamide derivative **11a** (35.7 mg, 73.8  $\mu\text{mol}$ , 41%) as a colorless foam and as an inseparable 1:1 diastereomeric mixture.  $R_f$  (**11a**) = 0.23 (hexanes:ethyl acetate 3:7). Diastereomer 1:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  = 1.23 (m, 3 H), 1.31 (d,  $J$  6.5 Hz, 1 H), 1.39 (m, 2 H), 1.53 (m, 2 H), 1.66 (s, 3 H), 2.01 (m, 2 H), 2.27–2.49 (m, 4 H), 3.88 (dd,  $J$  17.3, 5.5 Hz, 1 H), 3.91–4.17 (m, 3 H), 4.77–5.01 (m, 3 H), 5.03 (s, 1 H), 5.15 (d,  $J_5$  = 17.3 Hz, 1 H), 5.23 (d,  $J$  10.0 Hz, 1 H), 5.74 (m, 1 H), 6.59–6.78 (m, 2 H), 7.33–7.40 (m, 5 H) ppm.  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz):  $\delta$  = 15.8 (q), 18.2 (q), 19.9 (q), 23.4 (t), 27.0 (t), 33.3 (t), 34.4 (t), 35.3 (t), 42.6 (t), 47.2 (d), 49.7 (t), 63.4 (d), 72.7 (d), 119.2 (t), 126.0 (d), 126.3 (d), 128.8 (d), 129.2 (d), 129.9 (s), 131.3 (d), 133.6 (s), 167.6 (s), 168.9 (s), 169.2 (s), 172.4 (s) ppm. Diastereomer 2:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  = 1.23 (m, 3 H), 1.34 (d,  $J$  6.5 Hz, 3 H), 1.39 (m, 2 H), 1.53 (m, 2 H), 1.66 (s, 3 H), 2.01 (m, 2 H), 2.27–2.49 (m, 4 H), 4.23 (dd,  $J$  17.8, 6.8 Hz, 1 H), 3.91–4.17 (m, 3 H), 5.28–5.43 (m, 3 H), 5.03 (s, 1 H), 5.39 (m, 2 H), 5.74 (m, 1 H), 6.22 (m, 1 H), 6.70 (m, 1 H), 7.33–7.40 (m, 5 H) ppm.  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz):  $\delta$  = 16.2 (q), 18.8 (q), 19.9 (q), 23.4 (t), 27.0 (t), 32.8 (t), 35.4 (t), 35.2 (t), 42.2 (t), 47.2 (d), 49.7 (t), 63.4 (d), 71.8 (d), 119.2 (t), 126.0 (d), 126.3 (d), 128.8 (d), 129.2 (d), 129.9 (s), 131.3 (d), 133.3 (s), 167.2 (s), 168.9 (s), 169.2 (s), 172.6 (s) ppm. HRMS (CI) calc. for  $\text{C}_{27}\text{H}_{38}\text{N}_3\text{O}_5^+$   $[\text{M}+\text{H}]^+$ : 484.2806, found 484.2809.

***N*-tert-Butoxycarbonyl-(S)-alanyl-(N-methyl-naphthylglycyl)-glycine (2S,5E)-10-(tert-butyldimethylsiloxy)-5-methyl-dec-5-en-2-yl ester (12e).** According to **8a** methyl ester **7e** (251 mg, 0.57 mmol) in THF/MeOH (3:1, 2.8 mL) was saponified with a solution of LiOH (25.7 mg, 0.60 mmol) in  $\text{H}_2\text{O}$  (1.9 mL). The crude acid (dr 1:1) was directly used without further purification. For that, the acid (253 mg, 570  $\mu\text{mol}$ ) and alcohol **(S)-2** (204 mg, 0.68 mmol) were dissolved in dichloromethane (4.6 mL) and the solution was cooled to 0 °C before DCC (140 mg, 0.68 mmol) and DMAP (83.1 mg, 0.68 mmol) in dichloromethane (1.7 mL) were added. The reaction mixture was warmed to room temperature overnight, diluted with ethyl acetate (20 mL) and washed with sat.  $\text{NaHCO}_3$  and 1N  $\text{KHSO}_4$ , dried ( $\text{Na}_2\text{SO}_4$ ) and the solvent was evaporated *in vacuo*. Flash chromatography (silica, hexanes:ethyl acetate 6:4) provided tripeptide ester **12e** (305 mg, 0.42 mmol, 74%) as a 1:1 diastereomeric mixture. In addition, alcohol **(S)-2** (72.3 mg, 0.24 mmol, 35%) could be recovered.  $R_f$  (**12e**) = 0.23 (hexanes:ethyl acetate 6:4). Diastereomer 1:  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 0.05 (s, 6 H), 0.89 (s, 9 H), 1.26 (d, 3 H), 1.34 (d, 3 H), 1.42 (m, 2 H), 1.45 (s, 9 H), 1.51 (m, 2 H), 1.58 (s, 3 H), 1.67 (m, 2 H), 1.94–2.03 (m, 4 H), 2.95 (s, 3 H), 3.59 (m, 2 H), 4.02 (m, 1 H), 4.18 (m, 1 H), 4.67 (dq, 1 H), 4.95 (tq, 1 H), 5.12 (m, 1 H), 5.47 (m, 1 H), 6.25 (m, 1 H), 6.50 (s, 1 H), 7.40 (m, 1 H), 7.49–7.56 (m, 2 H), 7.81–7.90 (m, 3 H), 7.95 (s, 1 H), ppm.  $^{13}\text{C}$

NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = -5.3 (q), 15.9 (q), 18.3 (q), 18.4 (q), 19.9 (q), 26.0 (t), 26.0 (q), 27.7 (t), 28.4 (q), 32.2 (t), 32.5 (q), 34.1 (t), 35.4 (t), 41.6 (t), 46.8 (d), 60.9 (d), 63.2 (t), 69.7 (t), 72.6 (d), 78.3 (s), 125.2 (d), 126.7 (d), 127.6 (d), 128.2 (d), 128.7 (s), 129.1 (s), 131.1 (s), 133.2 (s), 169.1 (s), 171.8 (s), 171.8 (s) ppm. Diastereomer 2 (selected signals): <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 0.06 (s, 6 H), 0.90 (s, 9 H), 1.25 (d, 3 H), 1.59 (s, 3 H), 2.98 (s, 3 H), 6.53 (s, 1 H), 6.73 (m, 1 H) ppm. HRMS (CI) calc. for C<sub>40</sub>H<sub>66</sub>N<sub>3</sub>O<sub>7</sub>Si<sup>2+</sup> [M+H]<sup>+</sup>: 727.4581, found 727.4593.

***N*-tert-Butoxycarbonyl-(*S*)-alanyl-(*N*-methyl-naphthylglycyl)-glycine (2*S*,5*E*)-10-carboxy-5-methyl-dec-5-en-2-yl ester (13e):** Silylester **12e** (337 mg, 0.460 mmol) was dissolved in THF (1.4 mL) before TBAF·3 H<sub>2</sub>O (163 mg 0.510 mmol) in H<sub>2</sub>O (1.0 mL) was added. The reaction was monitored by TLC and after completion aqueous workup provided the corresponding alcohol which was directly subjected to Jones oxidation. For that, the alcohol (234 mg, 0.380 mmol) was dissolved in acetone (2.7 mL) before Jones reagent (3M, 380  $\mu$ L, 1.14 mmol) was added at 0 °C. Stirring was continued for 20 min before H<sub>2</sub>O (5 mL) was added. Ethyl acetate was added and the aqueous layer was extracted twice with ethyl acetate. The combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>) and the solvent was evaporated *in vacuo*. Flash chromatography (silica, hexanes:ethyl acetate 1:1 + 1% AcOH) provided acid **13e** (162 mg, 0.259 mmol, 68%) as a 58:42 diastereomeric mixture. R<sub>f</sub> (**13e-1**) = 0.36, R<sub>f</sub> (**13e-2**) = 0.31 (hexanes:ethyl acetate 1:1 + 1% AcOH). Diastereomer 1: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 1.24 (m, 3 H), 1.31 (d, 3 H), 1.44 (s, 9 H), 1.57 (s, 3 H), 1.59–1.78 (m, 4 H), 1.96–2.07 (m, 4 H), 2.28 (m, 2 H), 2.95 (s, 3 H), 3.97 (m, 1 H), 4.16 (dd, 1 H), 4.70 (m, 1 H), 4.92 (m, 1 H), 5.08 (t, 1 H), 5.71 (d, 1 H), 6.55 (s, 1 H), 7.14 (m, 1 H), 7.37 (d, 1 H), 7.46–7.54 (m, 2 H), 7.78–7.89 (m, 3 H), 7.92 (s, 1 H) ppm. <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 15.8 (q), 18.2 (q), 20.0 (q), 24.6 (t), 27.0 (t), 28.3 (q), 32.4 (q), 32.4 (t), 33.3 (t), 35.4 (t), 41.5 (t), 46.9 (d), 61.2 (d), 72.1 (d), 79.6 (s), 124.1 (d), 126.5 (d), 126.5 (d), 126.5 (d), 127.6 (d), 127.6 (d), 127.6 (d), 128.2 (d), 128.5 (s), 129.0 (s), 133.1 (s), 134.9 (s), 155.2 (s), 169.1 (s), 169.3 (s), 174.4 (s), 177.9 (s) ppm. Diastereomer 2 (selected signals): <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 1.39 (d, 3 H), 1.56 (s, 3 H), 2.26 (m, 2 H), 3.92 (m, 1 H), 4.22 (m, 1 H), 5.07 (t, 1 H), 5.65 (m, 1 H), 6.51 (s, 1 H), 6.65 (m, 1 H), 7.39 (d, 1 H) ppm. <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 15.7 (q), 18.4 (q), 20.1 (q), 24.7 (t), 27.1 (t), 33.2 (t), 41.6 (t), 60.8 (d), 72.3 (d), 80.0 (s), 124.0 (d), 126.4 (d), 126.7 (d), 126.7 (d), 127.5 (d), 127.5 (d), 127.5 (d), 128.7 (s), 128.9 (s), 133.1 (s), 134.8 (s), 155.7 (s), 169.2 (s), 169.5 (s), 169.5 (s) 177.9 (s) ppm.

**(9*S*,19*S*,5*E*)-6-(Naphthalene-2-yl)-7,9,16,19-tetramethyl-1-oxa-4,7,10-triazacyclononadec-15-en-2,5,8,11-tetraon (14e).** According to **11a** acid **13e** (162 mg, 259  $\mu$ mol) and pentafluorophenol (52.4 mg, 285  $\mu$ mol) in dichloromethane (2.6 mL) were reacted with EDC·HCl (54.6 mg, 285  $\mu$ mol). After workup as usual the pentafluorophenyl ester obtained was dissolved in dichloromethane (2.1 mL) before trifluoroacetic acid (0.50 mL) was added. After complete deprotection dichloromethane (1 mL) was added and the solution was added dropwise to a 7:1 suspension CHCl<sub>3</sub>/sat. NaHCO<sub>3</sub> (104 mL) over a period of 60 min at 40 °C. Workup as usual and flash chromatography (silica, hexanes:ethyl acetate 1:1, 4:6, 3:7) provided cyclic peptide **14 e** (59.9 mg, 118  $\mu$ mol, 46%) as a colorless foam and a 78:22 diastereomeric mixture. R<sub>f</sub> (**14e-1**) = 0.21, R<sub>f</sub> (**14e-2**) = 0.17 (hexanes:ethyl acetate 3:7). Diastereomer 1: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  = 1.28 (d, 3 H), 1.43 (d, 3 H), 1.61 (s, 3 H), 1.63-1.89 (m, 4 H), 1.93-2.16 (m, 4 H), 2.22 (m, 2 H), 2.86 (s, 3 H), 3.62 (dd, 1 H), 4.46 (dd, 1 H), 4.94-5.01 (m, 2 H), 5.11 (t, 1 H), 6.54 (s, 1 H), 6.88 (d, 1 H), 7.01 (m, 1 H), 7.42 (d, 1 H), 7.46-7.54 (m, 2 H), 7.81-7.89 (m, 3 H), 8.10 (s, 1 H) ppm. <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  = 15.8 (q), 17.6 (q), 19.6 (q), 25.5 (t), 26.2 (t), 31.5 (q), 32.9 (t), 34.6 (t), 35.2 (t), 41.2 (t), 46.0 (d), 59.3 (d), 71.4 (d), 125.3 (d), 126.3 (d), 126.4 (d), 126.5 (d), 127.5 (d), 128.3 (d), 128.4 (d), 128.9 (d), 130.7 (s), 132.9 (s), 133.1 (s), 134.4 (s), 169.2 (s), 169.9 (s), 173.1 (s), 173.5 (s). Diastereomer 2 (selected signals): <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  = 1.26 (d, 3 H), 1.57 (m, 3 H), 2.91 (s, 3 H), 4.05 (m, 1 H), 6.88 (d, 1 H), 7.36 (m, 1 H). HRMS (CI) calc. for C<sub>29</sub>H<sub>38</sub>N<sub>3</sub>O<sub>5</sub><sup>+</sup> [M+H]<sup>+</sup>: 508.2806, found 508.2829.

**(9S,19S,5E)-6-(4-Hydroxy-3-chlorophenyl)-7,9,16,19-tetramethyl-1-oxa-4,7,10-triazacyclononadec-15-en-2,5,8,11-tetraon (15d)**. The allyl protected cyclopeptide **14d** (17.0 mg, 31.0  $\mu\text{mol}$ ) was dissolved in dry MeOH (0.5 mL). Quinaldic acid (0.5 mg, 3.10  $\mu\text{mol}$ ,) as well as Ru-catalyst (1.4 mg, 3.10  $\mu\text{mol}$ ) were added at room temperature. After complete deprotection (LC-MS-control), DMSO (23  $\mu\text{L}$ , 330  $\mu\text{mol}$ ) was added and the solution was stirred overnight. The solvent was evaporated *in vacuo* and the crude product was purified by flash chromatography (silica gel,  $\text{CH}_2\text{Cl}_2/\text{Et}_2\text{O}$  1:1). Miureanamide derivative **15d** (12.0 mg, 23.6  $\mu\text{mol}$ , 76%) was obtained as a 1:1 diastereomeric mixture.  $R_f$  (**15d**) = 0.10 (dichloromethane/ $\text{Et}_2\text{O}$  1:1). Diastereomer 1:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 1.28 (d,  $J$  7.3 Hz, 3 H), 1.38 (d,  $J$  6.7 Hz, 3 H), 1.42-1.75 (m, 4 H), 1.58 (s, 3 H), 1.96-2.28 (m, 6 H), 2.84 (s, 3 H), 4.09 (m, 1 H), 4.67 (m, 2 H), 5.05-5.18 (m, 4 H, 1-H), 6.32 (s, 1 H), 6.97 (m, 1 H), 7.16 (m, 1 H), 7.34 (m, 1 H), 7.42 (m, 1 H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 15.5 (q), 16.4 (q), 20.0 (q), 25.6 (t), 26.2 (t), 29.7 (q), 32.0 (t), 34.8 (t), 34.9 (t), 41.4 (t), 46.0 (d), 60.4 (d), 72.4 (d), 116.5 (d), 120.2 (s), 125.2 (d), 128.1 (d), 130.2 (s), 131.0 (s), 136.8 (s), 151.6 (s), 168.4 (s), 168.8 (s), 174.1 (s), 174.5 (s). Diastereomer 2 (selected signals):  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 1.22 (d,  $J$  6.3 Hz, 3 H), 1.39 (d,  $J$  7.3 Hz, 3 H), 1.65 (s, 3 H), 7.66 (bs, 1 H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 20.0 (q), 31.7 (t), 40.9 (t), 46.1 (d), 60.9 (d), 71.6 (d), 116.6 (d), 130.8 (s), 168.5 (s), 169.5 (s), 174.5 (s). HRMS (CI) calc. for  $\text{C}_{25}\text{H}_{35}\text{ClN}_3\text{O}_6^+$   $[\text{M}+\text{H}]^+$ : 508.2209, found 508.2180.

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## Supplementary Material

General procedures and analytical data of all new compounds.

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