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FULL PAPER

Synthesis and biological evaluation of (modified) miuraenamides

Sarah Kappler,[a] Lisa Karmann,[a] Cynthia Prudel,[a] Jennifer Herrmann,[b] Giulia Caddeu,[c] Rolf Müller,[b] Angelika M. Vollmar,[c] Stefan Zahler [c] and Uli Kazmaier*[a]

Abstract: Miuraenamides, secondary metabolites of the marine myxobacterium *Paraliomyxa miuraensis* do not only show a high structural similarity to other cyclodepsipeptides isolated from sponges or terrestrial myxobacteria but they also exhibit a similar mode of action. They accelerate nucleation and polymerization of actin, and therefore interfere with cell division processes, at concentrations in the low nanomolar range. A late stage peptide modification allows the synthesis of a library of (simplified) miuraenamide derivatives with different halogenation and substitution pattern. Detailed SAR studies indicate, that bromination of the central tyrosine is essential for good biological activity, while the side chain of the *C*-terminal amino acid can be varied or can even be removed.

Introduction

Myxobacteria are highly interesting Gram-negative δ-proteobacteria found widespread all over the globe, living on the bark of trees, herbivore dung or decaying plants, using cellulose as foodstuff.[1] In addition, as gliding bacteria they can also hunt for food, especially other microorganisms such as fungi or bacteria.[2] One of the most impressive characteristics is the formation of complex fruiting bodies under starvation conditions.[3] In addition, their rich secondary metabolism is worth mentioning, making them one of the best natural product producers.[4] Myxobacteria were initially considered as terrestrial microorganisms but also a lot of marine representatives have been discovered during the last years.[5]

In 2006, Lizuka *et al*. isolated a novel, lightly halophilic myxobacterium, called *Paraliomyxa miuraensis*, from a soil sample at the coast of the Japanese island Miura.[6] Phylogenetic analysis showed an identity of 93.0-93.3% to two other species, *Nannocystis exedens* DSM 71 and *Enhygromyxa salina* JCM 11769. Interestingly, the authors did not mention the formation of fruiting bodies by this strain during cultivation. Investigating the secondary metabolites produced by this species resulted in the isolation of miuraenamides A and B[6] and two years later also of the derivatives C-F (Figure 1).[7]

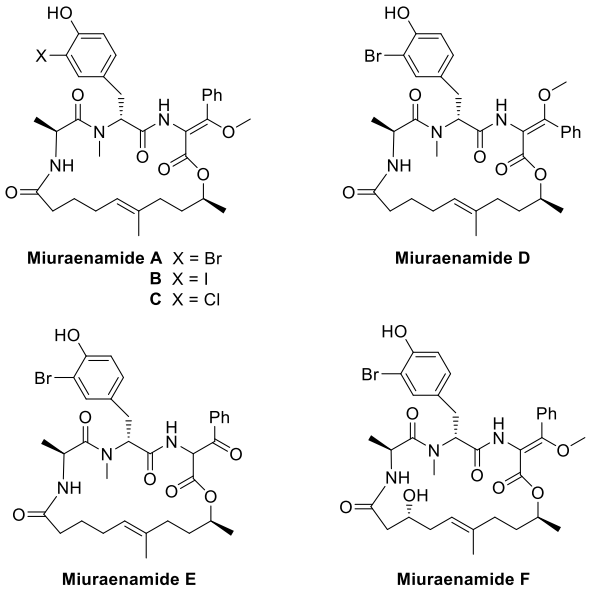

Figure 1. Natural occurring miuraenamides

Like many other cyclodepsipeptides the miuraenamides can be divided into two major building blocks. A tripeptide containing a

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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 motif. This part is not very common in marine natural products, but is also found in antifungal compounds such as the strobilurins and melithiazols.[8]

Indeed, activity was observed for miuraenamide A against *Candida rugosa* and this activity was proposed to result from an inhibition of the mitochondrial cytochrome *bc1* complex, as reported for other compounds containing the methoxyacryl pharmacophore. Therefore, it is not surprising that the antifungal activity depends strongly on this subunit. Miuraenamide D, with the opposite olefin geometry was found to be less active by factor 40, while the antifungal activity of the ketone derivative miuraenamide E was even worse (400-fold less active than miuraenamide A). Interestingly, the halogenation pattern had no significant influence. No antibacterial activity was observed, but miuraenamide A was found to stabilize actin filaments in tumor cells.[9] Unfortunately, the other derivatives were obtained only in tiny amounts, so that no detailed investigations of their biological activity was possible.

The strong interaction with the actin skeleton is not really surprising with respect to the close structural relationship of the miuraenamides to other cyclodepsipeptides (Figure 2) such as the geodiamolides,[10] seragamide,[11] pipestelide A,[12] or jasplakinolide.[13] All these natural products have been isolated from sponges, but probably they are not produced by them but are also secondary metabolites from bacteria living in them. [7]

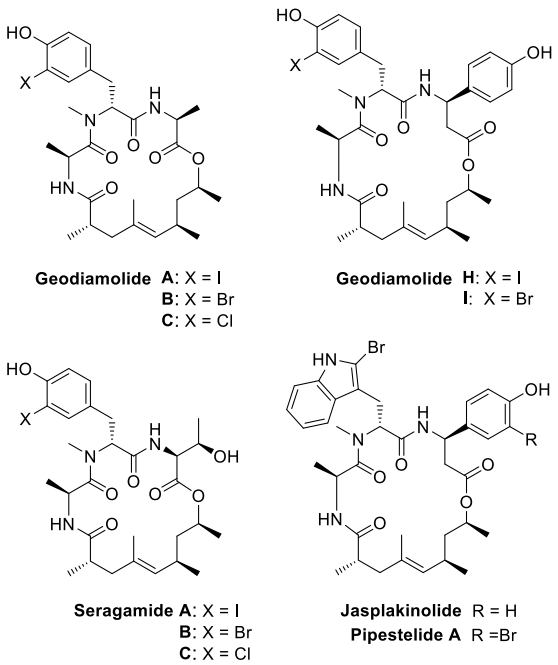
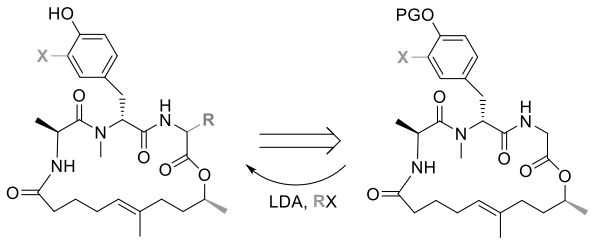


Figure 2. Structurally related cyclodepsipeptides from sponges

All these cyclodepsipeptides contain the same C-8 polyketide fragment and a tripeptide fragment containing an alanine, an *N*-methylated halogenated aromatic amino acid and an α- or β-amino acid at the *C*-terminus. All in marine surroundings 'common' halogens are incorporated into the central tyrosine, and the rings are either 18- or 19-membered. The same is true for the miuraenamides, but their structure is significantly simpler, especially in the polyketide part. While the other natural products contain six to seven stereogenic centres, the miuraenamides contain only three asymmetric C-atoms (and one stereoisomeric double bond). Therefore, the miuraenamides are ideal candidates for the development of potential anti-tumor drugs.

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.[14] Jasplakinolide was found to initiate actin polymerization and stabilizes already formed actin microfilaments, which causes significant morphological changes in the cell.[15] The same effects were also observed for the geodiamolides.[14] Interestingly, geodiamolide H showed cytotoxic effects towards a range of tumor cell lines, while geodiamolide I was inactive. [16] The interesting mode of action initiated several synthetic approaches towards jasplakinolide[17] and geodiamolide,[18] while the other cyclodepsipeptides have not been synthesized so far. Recently, we published the first synthesis of the miuraenamides A, D and E,[19] while the group of Suenaga reported also another synthetic protocol towards miuraenamides A and D one year later.[20] In their synthesis, the unusual unsaturated C-terminal amino acid was synthesized first and was incorporated into the growing peptide chain. No question, this approach is straightforward for the synthesis of the natural products themselves, but it is limited with respect to the synthesis of derivatives for structure-activity relationship (SAR) studies. Having a closer look at the cyclodepsipeptides shown in Fig. 2, thewerstern part of the peptide (*N*-terminus) seems to be rather conserved, while the *C*-terminus is relatively flexible, especially taking into account, that both isomers (miuraenamide A and D) are found in nature. The olefin geometry has a significant influence on the antifungal activity, but not on the cytotoxicity. Both isomers are almost equipotent.[19] Therefore, we designed our synthesis in such a way, that this unusual amino acid is incorporated in almost the last step. For this late stage modification, the corresponding glycine peptide is converted into a cyclic glycine ester enolate, which should provide a wide range of miuraenamide derivatives by trapping this enolate with various types of electrophiles (Scheme 1). Using this approach, we were interested to investigate the influence of the halogenation pattern, the *C*-terminal side chain as well as the configuration of the methyl group in the polyketide fragment on the cytotoxicity of the miuraenamide derivatives.



Scheme 1. Variations on the miuraenamide skeleton (in grey)

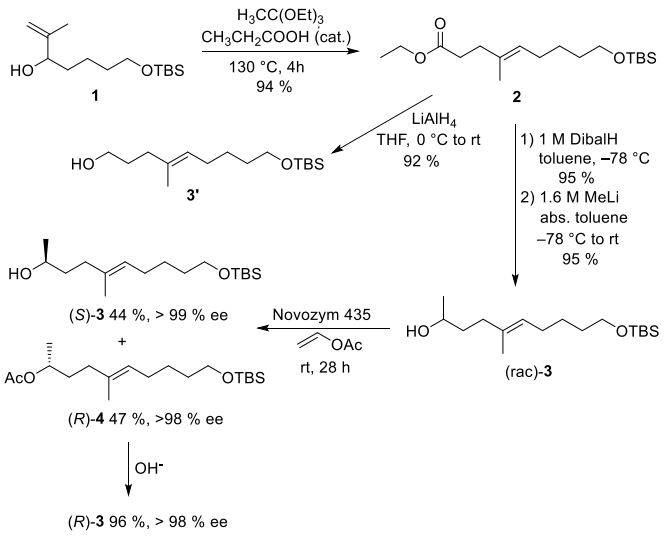
Results and Discussion

Since more than two decades our group is involved in the synthesis of peptidic natural products[21] and we are developing new synthetic protocols for unusual amino acids *via* modifications of chelated glycine ester enolates.[22] These enolates are on one hand thermally rather stable because of chelate complex formation, but on the other hand they show the high reactivity of metal enolates. The enolates undergo a wide range of reactions, such as alkylations, aldol[23] or Michael additions,[24] epoxide opening[25] or transition metal catalyzed allylic alkylations,[26] allowing the introduction of almost "every" side chain, often in a highly selective fashion. If the reactions are carried out with peptide esters or

amides, the stereochemical outcome can be controlled by the stereogenic centres in the peptide chain.[27] According to this protocol, we wanted to modify the *C*-terminus of the miuraenamide tripeptide (Scheme 1).

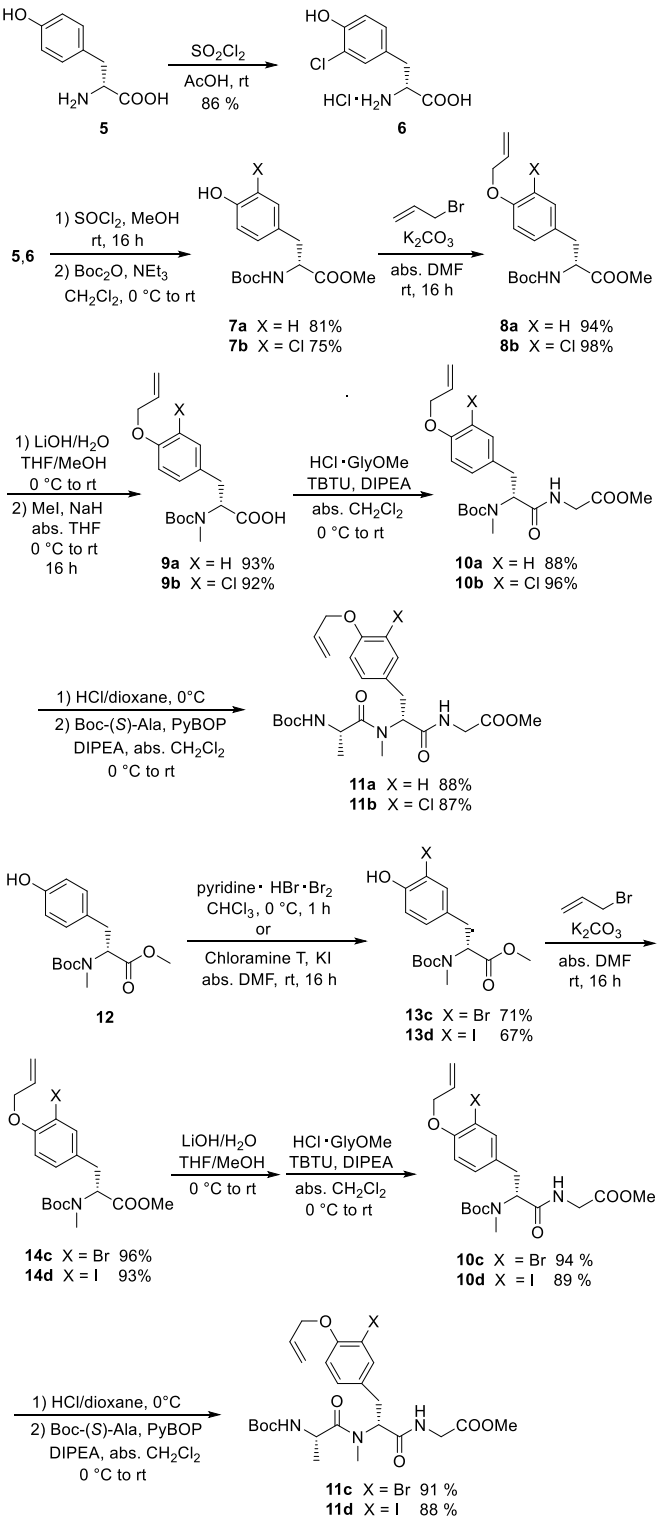
In this case, the stereochemical outcome of the modification step is of minor importance, because in case the stereoisomeric products can be separated, both isomers can be investigated separately, and in case one is more active than the other one it can also be synthesized in a conventional way.

Compared to the other cyclodepsipeptides (Figure 2) the polyketide fragment of the miuraenamides is by far the simplest one and its synthesis is straightforward (Scheme 2). The key step is a Johnson-Claisen rearrangement of allyl alcohol **1** towards ester **2**.[19] Direct reduction of **2** gives access to primary alcohol **3'** which can be used for the synthesis of miuraenamides without the methyl group in the polyketide (series C). DibalH reduction of **2** and addition of MeLi provides racemic secondary alcohol **3,** which on enzymatic kinetic resolution with Novozym gives access to (*S*)-**3** which is used for the natural miuraenamide derivatives (series A), while saponification of the (*R*)-acetate **4** provides (*R*)-**3** which was incorporated into the miuraenamides with inverted polyketide centre (series B).[19] In principle (*R*)-**3** can be interconverted into (*S*)-**3** *via* Mitsunobu reaction/saponification without loss of optical purity.



Scheme 2. Synthesis of polyketide precursors **3** and **3'**

For the synthesis of suitable protected tripeptides we used two different approaches (Scheme 3). The non-halogenated and chlorinated tripeptides were obtained from (*R*)-tyrosine (**5**) which was mono-chlorinated with SO_2Cl_2 in good yield.[28] Subsequent esterification and Boc-protection of **5** and **6**, followed by allylation of the phenol OH-group provided the fully protected tyrosine derivatives **8a** and **8b**. For the introduction of the *N*-methyl group, the methylester was saponified and after deprotonation of the amide functionality, it was methylated in excellent yield over both steps. Best results in the subsequent coupling with glycine esters were obtained with TBTU and diisopropylethylamine (DIPEA) as a base, while PyBOP was found to be the reagent of choice for the coupling of the Boc-(*S*)-Ala to the *N*-methylated terminus of the dipeptide. The syntheses of the brominated tripeptides **11c** and **11d** started from literature-known **12**.[29] Monobromination was carried out with pyridinium bromide perbromide,[30] while chloramin-T and KI was used to introduce the iodine into the phenyl ring.[31] Subsequent *O*-allylation provided the fully protected tyrosine derivatives **14c** and **14d**. Subsequent saponification and coupling with glycine ester using the TBTU protocol gave rise to the dipeptides **10c** and **10d**. Prolongation towards the tripeptides **11c** and **11d** in analogy to the previous couplings proceeded in comparable yields.



Scheme 3. Synthesis of the desired glycine tripeptides **11**

With these four tripeptides in hand, we next investigated the synthesis of the linear peptide-polyketide conjugates and the cyclization towards the glycine-miuraenamides (Table 1).

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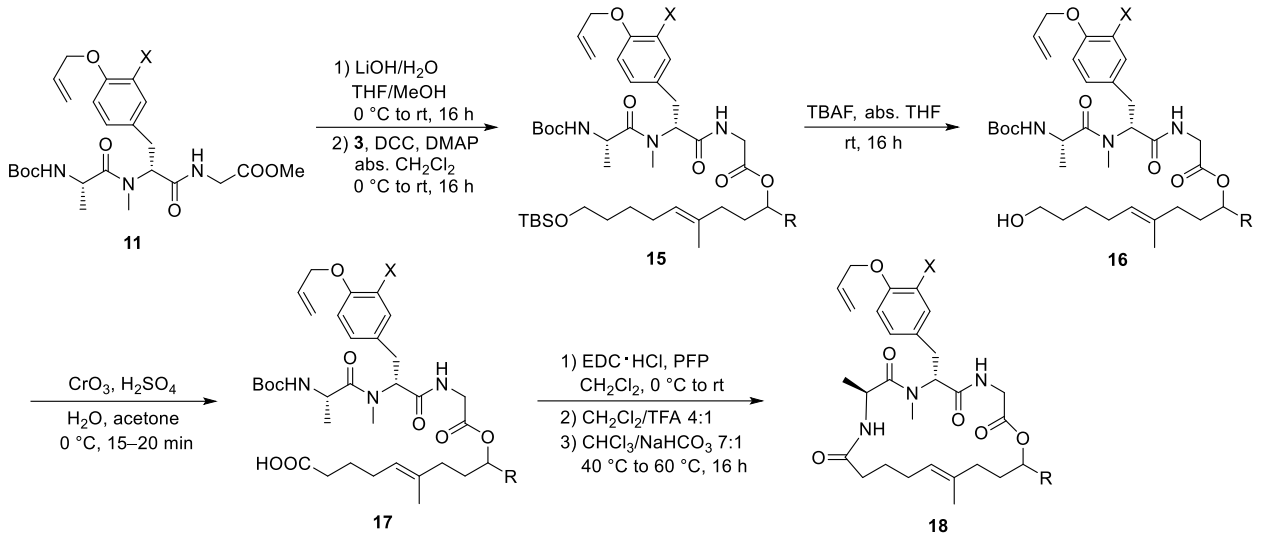
Table 1. Synthesis of the glycine cyclodepsipeptides **18**

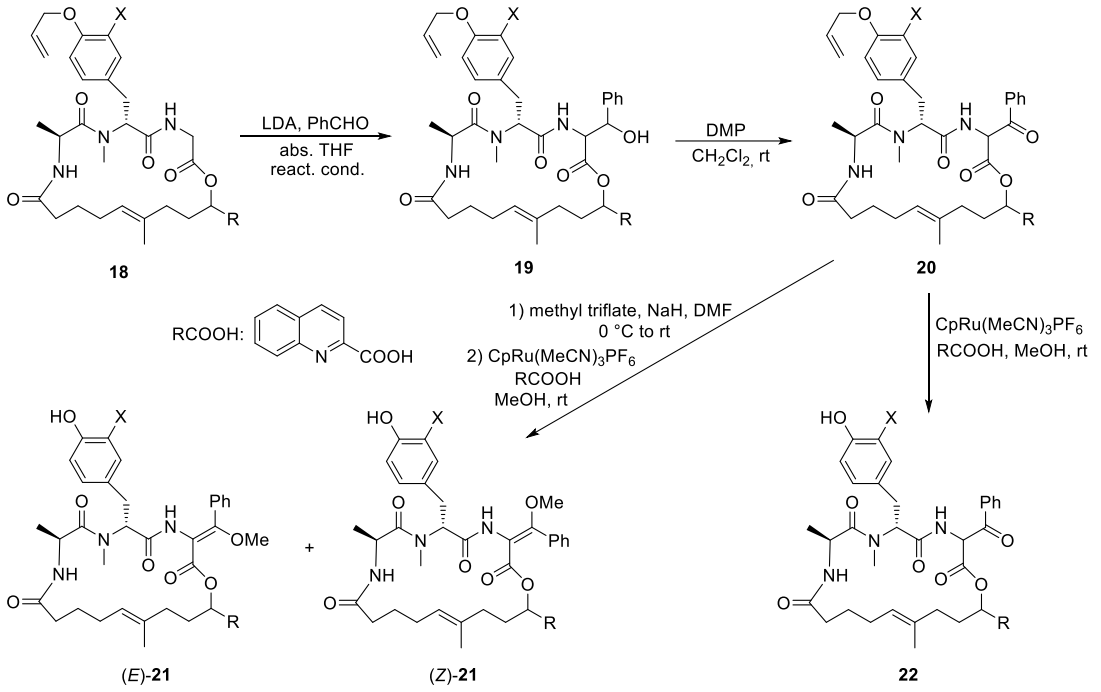


Entry	11	X	3	R	15	Yield [%]	16	Yield [%]	17	Yield [%]	18	Yield [%]
1	**11a**	H	(*S*)-**3**	◄	**15aA**	67	**16aA**	92	**17aA**	64	**18aA**	63
2	**11b**	Cl	(*S*)-**3**	◄	**15bA**	87	**16bA**	90	**17bA**	53	**18bA**	59
3	**11c**	Br	(*S*)-**3**	◄	**15cA**	78	**16cA**	86	**17cA**	76	**18cA**	55
4	**11d**	I	(*S*)-**3**	◄	**15dA**	71	**16dA**	84	**17dA**	59	**18dA**	59
5	**11b**	Br	(*R*)-**3**	····	**15cB**	82	**16cB**	88	**17cB**	68	**18cB**	45
6	**11b**	Br	**3'**	H	**15cC**	82	**16cC**	83	**17cC**	37	**18cC**	42

All four tripeptides **11** were coupled with the secondary alcohol (*S*)-**3** with the "correct" configuration in the polyketide (series A), while only the brominated peptide **11c** was coupled also with the other two alcohols (entries 5 and 6, series B and C). The yields of the different reaction steps are summarized in Table 1. Saponification of the tripeptides **11** and subsequent esterification according to the Steglich protocol[32] delivered the desired peptide esters **15** in generally good yield. It is recommended to use a slight excess of the alcohol (1.2-1.3 equiv.) for reproducible good yields. The subsequent cleavage of the silyl protecting group to **16** was also not a serious issue, but the subsequent oxidation towards the desired carboxylic acid caused some problems at the beginning. While oxidation, e.g. with Dess Martin periodinane[33] proceeded cleanly, the further oxidation, e.g. *via* Lindgren-Pinnick oxidation[34] was not successful, even when a scavenger was used. The major problem was the addition of hypochloric acid formed toward on the threefold substituted double bond in the polyketide fragment, clearly indicating that this motif is sensitive towards acidic conditions. Also other oxidation reagents such as CrO_3/pyridine, pyridinium chlorochromate or TEMPO gave unsatisfying results. So far, the best yields of **17** could be obtained with CrO_3/H_2SO_4 (Jones oxidation) even under these acidic conditions. This reaction is very fast and one has to catch the best moment, when almost all starting material is consumed and side reactions (Boc-deprotection and addition toward the double bond) are not yet a serious issue. The acid lability of the double bond is also not unproblematic in one of the next steps, the deprotection of the Boc-protecting group during ring closure. We decided to use Schmidt's pentafluorophenylester method for this approach since it allows a separate activation of the carboxyl terminus and an *N*-deprotection under high dilution conditions.[35] For the activation, we used EDC, because it can easily be removed *via* aqueous workup. Subsequently, the *N*-Boc protecting group was removed with TFA in CH_2Cl_2 (1:4). After complete deprotection the solution was diluted with $CHCl_3/NaHCO_3$ (c = 0.0025 M). Under these conditions reproducible yields in the range of 60 ± 5% were obtained for the derivatives of the A series, while the derivatives **18cB** and **18cC** with the "unnatural" polyketide gave slightly lower yields but still in a preparative useful range. It should be mentioned that replacing the Boc-protecting group by an Fmoc group to avoid side reactions during the acidic cleavage did not result in better overall yields.

With these cyclodepsipeptides **18** in hand, we next focused on the introduction of different side chains at the *C*-terminal amino acid of the tripeptide. To get access to the natural products themselves a benzoylation at this position seems to be appropriate. In principle, such α-amino-β-ketoesters can directly be obtained by trapping a glycine enolate either with acyl halides or esters,[36] but first attempts provided only yields around 20%. Therefore, we decided to investigate a two-step approach of aldol addition/oxidation. The stereochemical outcome of the aldol reaction does not play any role here, since the stereogenic centres are removed afterwards during oxidation and the β-keto amino acid can epimerize to the natural configured cyclic peptide. During previous studies, we observed that the yields of aldol reactions can be increased by using LDA as a base in excess. This is in agreement with observations made by Seebach *et al*. who reported that the solubility of polylithiated peptides at low temperature increased with an excess of LDA.[37] Addition of 5 equiv. of LDA towards the cyclodepsipeptides **18aA** and **18cA** resulted in the formation of a dark red enolate solution. 2 equiv. of benzaldehyde were added after 10 min at -78 °C and the reaction mixture was stirred vigorously and slowly warmed up in the cooling bath. After 90 min the reactions were quenched at low temperature and the desired aldol products could be obtained in good yields as diastereomeric mixtures (Table 2, entries 1 and 2).

Table 2. Synthesis of miuraenamides and derivatives **21** and **22**



Entry	18	X	R	Reaction conditions	19	Yield [%]	20	Yield [%]	diast. ratio	21	Yield [%]	ratio *E*:*Z*	22	Yield [%]	diast. ratio
1	**18aA**	H	◄	–78 °C to –60 °C, 90 min	**19aA**	63[a]	**20aA**	83[a]	93:7	**21aA**	48	3:1	**22aA**	[b]	-
2	**18bA**	Cl	◄	–78 °C, 180 min	**19bA**	64	**20bA**	49	82:18				**22bA**	78	92:8
3	**18cA**	Br	◄	–78 °C to –70 °C, 90 min	**19cA**	66[c]	**20cA**	73[c]	91:9	**21cA**	73	3:1	**22cA**	10[d]	90:10
4	**18dA**	I	◄	–78 °C, 35 min	**19dA**	58	**20dA**	82	94:6				**22dA**	95	94:6
5	**18cB**	Br	····	–78 °C, 150 min	**19cB**	68[e]	**20cB**	86	76:24				**22cB**	91	76:24
6	**18cC**	Br	H	–78 °C, 210 min	**19cC**	71	**20cC**	36[f]	71:29						

[a] Contaminated with 10% enol ether. [b] Side product of **21aA**, but could not be isolated. [c] Contaminated with 2% enol ether. [d] Side product of **21cA**. [e] Contaminated with 4% enol ether. [f] Product is not stable and decomposes during storage.

Interestingly, the product was contaminated with some enol ether, resulting from an isomerization of the allyl protecting group under the basic reaction conditions.[38] This side reaction occurred during the relatively long reaction time and was more significant in case of the unhalogenated peptide **18aA** (10%) which was warmed to -60 °C, while only traces are found with the brominated **18cA** which was quenched at -70 °C. Therefore, the reaction of the iodinated peptide **18dA** (entry 3) was carried out at -78 °C and was quenched after 35 min. The yield was comparable, but no isomerization occurred under these conditions. Although the enol ether could not be separated at this stage, it was no problem to remove it later on after cleavage of the allyl protecting group. Subsequent Dess Martin oxidation of the aldol products **19** proceeded cleanly providing the desired ketones **20** in generally good yield. According to ^{1}H NMR the diastereomers are found in a ratio of 93:7 (± 2%) in $CDCl_3$, except for the chlorinated product **20bA** (entry 2). This ratio obviously is solvent dependent. In d_6-DMSO a ratio of 3:1 was observed, clearly indicating that the α-stereogenic centre can easily epimerize towards the most stable configuration in solution.

To finalize the synthesis of the brominated miuraenamides A, D and E, the ketone **20cA** had to be converted into the corresponding enol ether and the allyl protecting group had to be removed from the tyrosine (entry 3). The enol ether formation was not as easy as expected, and even with methyl triflate no complete conversion of the ketone could be observed and a mixture of (*E*)- and (*Z*)-enol ether with unreacted ketone was obtained. But since all three derivatives are found in nature, the crude mixture was subjected to allyl deprotection using $CpRu(MeCN)_3PF_6$ as a catalyst.[39] The obtained mixture of miuraenamides could be separated by preparative reverse phase HPLC providing miuraenamide A (47%) and miuraenamide E (10%) in pure form, while miuraenamide D was always contaminated with miuraenamide E, although according to HPLC a clean separation should be possible. Obviously, miuraenamide D hydrolyzes easily to miuraenamide E, much faster than miuraenamide A, and therefore we assume that the "natural" miuraenamide E might be an artefact of the isolation and workup. The enol ether formed during the aldol addition did not undergo cleavage, and therefore this side product could easily be removed on this stage.

The same observation was also made with the non-halogennated derivative **20aA** (entry 1). In this case, (*E*)- **21aA** could be obtained, while the (*Z*)-isomer was contaminated with the ketone **22aA**, which could not be isolated.

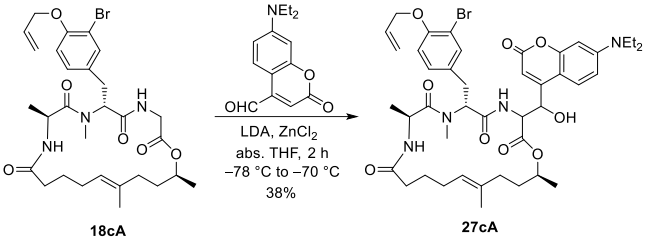
The configuration of the double bond in **21cA** was determined by H,H-NOESY-correlation. The major (*E*)-product showed clear couplings between the aromatic protons of the brominated tyrosine and the phenyl ring at the double bond, as well as interacttions of the methoxy group and the methyl group of the polyketide.

First investigations of the biological activity of the miuraenamides towards several cancer cell lines indicated that the double bond geometry obviously is not crucial and both isomers showed comparable activity, while the ketone was a little less active by factor 3-5, depending on the cell line. Because the enol ether formation was not a trivial issue and because of the stability

problems of the enol ethers, we decided to investigate the influence of the substitution pattern further on with the easier accessible and more stable ketones. Both, the chlorinated (entry 2) and iodinated ketones (entry 4), as well as the derivatives with the inverted and simplified polyketide chains (B, C) (entries 5 and 6), were obtained in an analogous way.. The relatively low yield observed for the primary ester **20cC** (entry 6) is caused by an instability of this compound, and complete decomposition is observed upon storage, even in the fridge.

During our previous studies on the closely related chondramides, we observed that incorporation of halogens into the *C*-terminal aromatic amino acid had a positive effect on the biological activity of these compounds,[40] so we decided to investigate the influence of halogens on the aryl ketone also in this case (Table 3). Although one might expect a higher reactivity of the halogenated benzaldehydes, we observed a significantly slower reaction. Even after prolonged reaction times and slightly increased temperature, no complete decolourization of the dark red enolate solution was observed. In some cases, the aldol products could not be separated from the starting material and therefore the crude reaction mixture was subjected to Dess Martin periodinane oxidation. The ketones were obtained in yields of 30-40% (for both steps) in all cases. Subsequent allyl-deprotection proceeded cleanly giving access to the desired dihalogenated miuraenamides **25** and **26**.

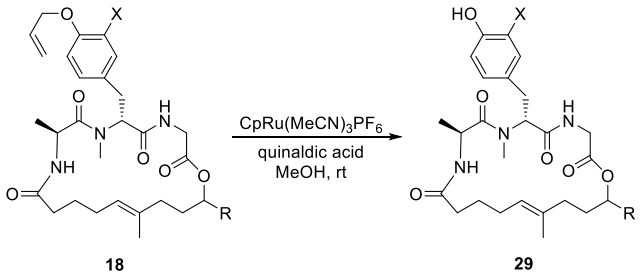
Since our group is also involved in the development of new techniques for the fluorescence labelling of amino acids and peptides[41] we decided to synthesize also a fluorogenic miuraenamide with a coumarine side chain (Scheme 4). Such a fluorogenic natural product should be helpful for live cell imaging, because the local binding in the cell can directly be observed by fluorescence microscopy. For this approach, a suitable substituted coumaryl carbaldehyde is required, which can easily be obtained from the corresponding triflate *via* vinylation/ozonolysis.[41c] Aldol reaction under the usual reaction conditions provided the desired β-hydroxylated derivative **27cA** in acceptable yield after preparative RP-HPLC. Since we failed to oxidize the aldol product to the corresponding ketone we decided to use **27cA** directly for the live cell imaging.



Scheme 4. Synthesis of a fluorogenic miuraenamide derivatibe **27**

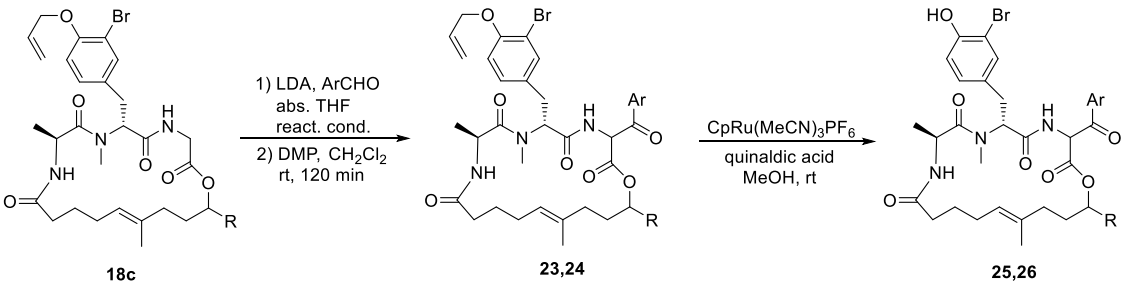
With respect to the fact that the side chain at the *C*-terminus obviously has only a minor influence on the biological activity, at least towards tumor cells, and that its introduction might cause some problems, we were interested to see if the side chain is required at all. Therefore, the allylated glycine peptides were subjected to deprotection giving rise to the rather simple cyclodepsipeptides containing only 2-3 stereogenic centres (Table 4).

Table 4. Synthesis of simplified miuraenamide derivitaves **29**



Entry	**18c**	X	R	**29**	Yield [%]
1	**18aA**	H	◄	**29aA**	90
2	**18bA**	Cl	◄	**29bA**	99
3	**18cA**	Br	◄	**29cA**	98
4	**18dA**	I	◄	**29dA**	99
5	**18cB**	Br	⋯	**29cB**	91
6	**18cC**	Br	H	**29cC**	99

Table 3. Synthesis of dihalogenated miuraenamide derivatives **25** and **26**



Entry	**18c**	R	Reaction conditions	ArCHO	**23,24**	Yield [%]	diast. ratio	**25,26**	Yield [%]	diast. ratio
1	**18cA**	◄	–78 °C, 150 min	*p*-Br-Ph	**23cA**	19	87:13	**25cA**	66	80:20
2	**18cA**	◄	–78 °C, 120 min	*p*-F-Ph	**24cA**	26	68:32	**26cA**	73	90:10
3	**18cB**	⋯	–65 °C, 180 min	*p*-Br-Ph	**23cB**	31[a]	75:25	**25cB**	80	70:30
4	**18cB**	⋯	–78 °C, 140 min	*p*-F-Ph	**24cB**	37	75:25	**26cB**	91	73:27
5	**18cC**	H	–65 °C, 120 min	*p*-Br-Ph	**23cC**	31[a]	79:21	**25cC**	95	79:21
6	**18cC**	H	–70 °C, 120 min	*p*-F-Ph	**24cC**	40[a]	78:22	**26cC**	99	72:28

The cytotoxicity of all new cyclic miuraenamide derivatives (**18**–**29**) was investigated using two human cancer cell lines, HCT-116 (colon cancer) and U-2 OS (osteosarcoma). The results are summarized in Table 5 ordered by protected and unprotected derivatives.

Table 5. Cytotoxicity of miuraenamides **18-29**

with *O*-protecting group

Entry	Derivative	HCT-116[a] IC_{50} [μM]	U-2 OS[a] IC_{50} [μM]	
1	**18aA**	109	56.1	
2	**18bA**	29.7	26.0	
3	**18cA**	1.1	n.d.	
4	**18dA**	8.1	7.3	
5	**18cB**	33.3	33.8	
6	**18cC**	2.9	2.4	
7	**19aA**	4.7	1.9	
8	**19bA**	0.39	0.18	
9	**19cA**	0.23	10.3	
10	**19cC**	1.72	0.69	
11	**19dA**	0.54	0.35	
12	**20aA**	19.2	16.5	
13	**20bA**	1.38	0.86	
14	**20cA**	0.42	9.5	
15	**20dA**	3.9	2.1	
16	**20cB**	8.0	11.7	
17	**20cC**	4.31	2.01	
18	**23cA**	1.27	0.62	
19	**23cB**	6.9	8.8	
20	**23cC**	6.7	2.3	
21	**24cA**	2.33	1.92	
22	**24cB**	4.5	5.6	
23	**24cC**	3.2	3.6	
24	**27cA**	2.1	1.7	

without *O*-protecting group

Entry	Derivative	HCT-116[a] IC_{50} [μM]	U-2 OS[a] IC_{50} [μM]	HUVEC[b] IC_{50} [μM]
25	(*E*)-**21aA**	0.05	1.14	
26	(*Z*)-**21aA**	1.37	9.57	
27	(*E*)-**21cA** (Miu A)	0.006	0.009	
28	(*Z*)-**21cA** (Miu D)	0.004	0.023	
29	**22bA**	0.096	0.096	
30	**22cA** (Miu E)	0.014	0.052	
31	**22dA**	0.013	0.006	
32	**22cB**	0.061	0.186	0.248
33	**25cA**	0.027	0.013	
34	**25cB**	0.037	0.136	0.066
35	**25cC**	0.011	0.046	
36	**26cA**	0.087	0.043	
37	**26cB**	0.123	0.160	
38	**26cC**	0.028	0.043	0.071
39	**29aA**	12.2	16.0	32.0
40	**29bA**	0.023	0.073	0.214
41	**29cA**	0.0012	0.0048	0.04
42	**29dA**	0.0065	0.011	0.128
43	**29cB**	1.61	2.00	
44	**29cC**	0.018	0.056	0.163

[a] Half-inhibitory concentrations (IC_{50}) were determined after 5 d incubation in an tetrazolium salt (MTT) reduction assay. [b] IC_{50} values were determined after 3 d incubation using crystal violet staining.

Although, the two different cancer cell lines showed some specific sensitivities towards single compounds, a general trend can be observed. The *O*-protected derivatives are significantly less active in comparison to the unprotected compounds, ranging from 100-fold in case of the miuraenamide E analogs (**20**, **23**, **24** *vs*. **22**, **25**, **26**) up to 1000-fold in case of the glycine-containing "miuraenamides light" (**18** *vs*. **29**). Obviously, the OH-functionality of the tyrosine is involved in the binding towards actin. This interaction is probably modulated by the halogens on the aromatic ring, because a strong influence of the halogenation pattern is also observed. In general, the bromo derivatives display most pronounced activity, followed by the iodo compounds, while derivatives with non-halogenated tyrosines are significantly less active (entries 1-4, 29-31). This effect is tremendous for the "miuraenamide light" derivatives **29** (39-42), where the bromo derivative **29cA** is the most active compound of the whole series (entry 41), while non-halogenated **29aA** is almost inactive (entry 39). This example illustrates that the substituent at the *C*-terminus does only play a minor role, because it can be removed completely, as long as the halogenation pattern of the tyrosine is correct. This unit seems to be essential for binding, while the *C*-terminal amino acids seems to be not involved at all. Therefore, very similar cytotoxicity values are obtained for a wide range of differently substituted miuraenamides, in the protected (entries 13-24) and unprotected series (entries 29-38). For example, the fluorogenic aldol product **27cA** (entry 24) was comparably active to fluorinated aryl ketone **24cA** (entry 21). However, removing the substituent completely makes the derivatives more sensitive to additional structural changes. Interconverting the stereogenic center in the polyketide causes a drop in activity by around 1500 (HCT-116) (entries 41/43), an effect which is only moderate in case of the ketones **22**, **25** and **26** (entries 14/17, 33-38). Removing the stereogenic center in the polyketide part completely is well accepted (entries 33/35, 36/38, 42/44).

For a subset of unprotected derivatives the effects on proliferation was tested in non-tumor cells (HUVECs). The IC_{50} values (Table 5) are by tendency higher than for the tumor cells due to the necessary experimental conditions. However, the overall potency in the different cellular setups correlates well.

An *in vitro* actin polymerization assay with pyrene labeled actin showed a shift of the curve of fluorescence intensity to the left and an increase of the slope with 10 μM **21cA** (miuraenamide A), indicating accelerated nucleation and polymerization of actin, as was to be expected for an actin nucleating and filament stabilizing compound (see Supporting Information, Fig. 1 A-E). At the same concentration (10 μM), some compounds had an effect similar to **21cA** (**22cC**, **26cC**; SI Fig. 1 A and B), no effect (**22cB**, **25cB**, **29bA**, **29cC**; SI Fig. 1 A, B, D and E) or even a paradoxical inhibitory effect (**27cA**, **29aA**, **29cA**, **29dA**, SI Fig. 1 C, D and E). When the concentrations of the compounds were normalized to the respective IC_{50} values of the cellular assay with HUVECs (IC_{50} from Table 5 x 1000), they showed nearly equipotent effects as compared to **21cA** (SI Fig. 2 A-D). This means that the differences in the potency of the derivatives is not due to uptake- or stability issues in the cellular assays, but results from different affinities to actin. For **27cA** and **29aA** this normalization was not possible due to solubility issues. The paradoxical effects of **29cA** and **29dA** at low concentrations, which are reversed at higher concentrations, could hint towards an additional high affinity binding site (responsible for an inhibition of polymerization) at the actin molecule addressed by these compounds, which is then overridden by lower affinity binding to a different binding site (responsible for the nucleation and polymerization effect).

Fluorogenic derivative **27cA** was also used to visualize binding of the miuraenamides towards actin (Figure 3). The fluorogenic derivative **27cA** does not bind to F-actin (Figure 3A) in the equimolar (2 µM) presence of phalloidin, most likely due to competition. But staining of F-actin (especially at the lamellipodia) is clearly visible in the absence of phalloidin (Figure 3B).

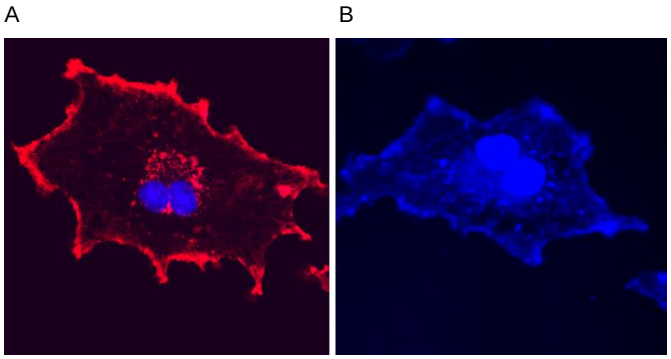


Figure 3. Confocal image of a HUVEC cell. **A**: F-actin stained with 2 µM rhodamine-phalloidin (red) and nuclei with Hoechst (blue). **B**: The fluorogenic derivative **27cA** shows excitation and emission characteristics similar to Hoechst. Therefore **27cA** (2 µM) shows up in the same fluorescence channel as Hoechst staining.

Conclusion

In conclusion, we could show that a rather simple cyclodepsipeptide is an ideal precursors for late-stage modifications and straightforward syntheses of miuraenamide derivatives. Detailed SAR studies indicate that the *C*-terminus of the tripeptide fragment allows a wide range of variations without affecting the high cytotoxicity of these derivatives significantly. Removing the side chain completely provides a highly active compound, which becomes more sensitive towards further structural modifications. Incorporation of a fluorogenic side chain allows the visualization of the binding towards actin, while the miuraenamides initiate and accelerate actin nucleation and filament stabilization.

Experimental Section

General remarks: All air- or moisture-sensitive reactions were carried out in dried glassware (>100 °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® SIL G/UV254). Visualization was accomplished with UV-light, Ceric Ammonium Sulfate solution, $KMnO_4$ solution or ninhydrin solution. Melting points were determined with a MEL-TEMP II (Laboratory Devices) melting point apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded with a Bruker AC-400 [400 MHz (^1H) and 100 MHz (^{13}C)]. Chemical shifts are reported in ppm relative to TMS or internal solvent. Mass spectra were recorded with a Finnigan MAT 95 spectrometer (quadrupole) using the CI technique.

(*R*)-(*O*-Allyl-*N*-*tert*-butoxycarbonyl-3-iodo-*N*-methyl-tyrosine methyl-ester (14d): Iodinated tyrosine **13d**[42] (2.42 g, 5.56 mmol, 1.0 eq) was dissolved in dry DMF (28 mL). Potassium carbonate (922 mg, 6.67 mmol, 2.0 eq) and allyl bromide (0.58 mL, 6.71 mmol, 2.0 eq) were added at room temperature. After stirring overnight, the reaction mixture was diluted with EtOAc and washed three times with H_2O. The organic layer was dried over Na_2SO_4. Column chromatography (silica gel, petroleum ether/EtOAc 8:2, 7:3) gave rise to the allyl protected tyrosine **14d** (2.46 g, 5.18 mmol, 93 %) as colorless, viscous oil. $[\alpha]_D^{20}$ = +53.8 (c = 1.0, $CHCl_3$). Major rotamer: ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.40 (s, 9 H), 2.74 (s, 3 H), 2.86 (dd, *J* = 14.6, 10.0 Hz, 1 H), 3.25 (dd, *J* = 14.4, 6.2 Hz, 1 H), 3.74 (s, 3 H), 3.87 (dd, *J* = 18.2, 4.2 Hz, 1 H), 4.16 (dd, *J* = 18.2, 6.6 Hz, 1 H), 4.55 (dt, *J* = 4.6 Hz, 1.3 Hz, 2 H), 4.89 (dd, *J* = 9.1, 6.3 Hz, 1 H), 5.29 (ddt, *J* = 10.6, 1.5, 1.5 Hz, 1 H), 5.49 (ddt, *J* = 17.3, 1.8, 1.8 Hz, 1 H), 6.03 (ddt, *J* = 17.1, 10.3, 4.8 Hz, 1 H), 6.69 (bs, 1 H), 6.71 (d, *J* = 8.4 Hz, 1 H), 7.15 (dd, *J* = 8.0, 2.0 Hz, 1 H), 7.61 (s, 1 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 28.3, 31.0, 32.5, 41.1, 52.3, 59.5, 69.8, 80.8, 86.5, 112.4, 117.6, 130.0, 131.9, 132.6, 139.8, 155.9, 156.6, 170.0, 170.8. Minor rotamer (selected signals): ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.32 (s, 9 H), 2.79 (s, 3 H), 3.32 (dd, *J* = 5.0 Hz, 1 H), 3.76 (s, 3 H), 3.99 (dd, *J* = 18.0, 3.9 Hz, 1 H), 4.78 (m, 1 H), 6.40 (bs, 1 H), 7.06 (d, *J* = 7.9 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 28.1, 30.6, 52.4, 61.3, 81.1, 86.9, 132.2, 139.7, 155.1, 155.9, 170.0, 170.5. HRMS (CI) calcd for $C_{21}H_{30}IN_2O_6^+$ $[M+H]^+$: 533.1143, found: 533.1109.

(*R*)-(*O*-Allyl-*N*-*tert*-butoxycarbonyl-3-iodo-*N*-methyl-tyrosyl)-glycine methyl ester (10d): Tyrosine methyl ester **14d** (3.58 g, 7.53 mmol, 1.0 eq) was dissolved in THF/MeOH (3:1, 60 mL) and a solution of LiOH (189 mg, 7.91 mmol, 1.05 eq) in dest. H_2O (15 mL) was added at 0 °C. After complete conversion (TLC-control), the solvent was evaporated *in vacuo* and the residue was acidified with 1 M HCl solution to pH 2. The aqueous layer was extracted with EtOAc, the combined organic layers were dried over Na_2SO_4 and the solvent was evaporated *in vacuo*.

To a solution of the crude acid (1.0 eq) and glycine methyl ester hydrochloride (1.04 g, 8.28 mmol, 1.1 eq) in dry CH_2Cl_2 (53 mL) DIPEA (2.69 mL, 15.8 mmol, 2.1 eq) and TBTU (2.66 g, 8.28 mmol, 1.1 eq) were added at 0 °C. After stirring overnight at room temperature, the solvent was evaporated *in vacuo* and the residue was dissolved with EtOAc. The organic layer was washed successively with 1 M $KHSO_4$-, saturated $NaHCO_3$-, and saturated NaCl-solution. After drying over Na_2SO_4, the desired dipeptide **10c** (3.56 g, 6.69 mmol, 89 %) was obtained by column chromatographie (silica gel, petroleum ether/EtOAc 1:1) as colorless, viscous oil. $[\alpha]_D^{20}$ = +53.8 (c = 1.0, $CHCl_3$). Major rotamer: ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.40 (s, 9 H), 2.74 (s, 3 H), 2.86 (dd, *J* = 14.6, 10.0 Hz, 1 H), 3.25 (dd, *J* = 14.4, 6.2 Hz, 1 H), 3.74 (s, 3 H), 3.87 (dd, *J* = 18.2, 4.2 Hz, 1 H), 4.16 (dd, *J* = 18.2, 6.6 Hz, 1 H), 4.55 (dt, *J* = 4.6 Hz, 1.3 Hz, 2 H), 4.89 (dd, *J* = 9.1, 6.3 Hz, 1 H), 5.29 (ddt, *J* = 10.6, 1.5, 1.5 Hz, 1 H), 5.49 (ddt, *J* = 17.3, 1.8, 1.8 Hz, 1 H), 6.03 (ddt, *J* = 17.1, 10.3, 4.8 Hz, 1 H), 6.69 (bs, 1 H), 6.71 (d, *J* = 8.4 Hz, 1 H), 7.15 (dd, *J* = 8.0, 2.0 Hz, 1 H), 7.61 (s, 1 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 28.3, 31.0, 32.5, 41.1, 52.3, 59.5, 69.8, 80.8, 86.5, 112.4, 117.6, 130.0, 131.9, 132.6, 139.8, 155.9, 156.6, 170.0, 170.8. Minor rotamer (selected signals): ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.32 (s, 9 H), 2.79 (s, 3 H), 3.32 (dd, *J* = 5.0 Hz, 1 H), 3.76 (s, 3 H), 3.99 (dd, *J* = 18.0, 3.9 Hz, 1 H), 4.78 (m, 1 H), 6.40 (bs, 1 H), 7.06 (d, *J* = 7.9 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 28.1, 30.6, 52.4, 61.3, 81.1, 86.9, 132.2, 139.7, 155.1, 155.9, 170.0, 170.5. HRMS (CI) calcd for $C_{21}H_{30}IN_2O_6^+$ $[M+H]^+$: 533.1143, found: 533.1109.

(*S*)-(*N*-*tert*-Butoxycarbonyl-alanyl)-(*R*)-(*O*-allyl-3-iodo-*N*-methyl-tyrosyl)-glycine-methyl ester (11d): To the Boc-protected dipeptide **10d** (3.91 g, 7.34 mmol, 1.0 eq) a 4 M HCl/dioxane-solution (18.4 mL, 73.4 mmol, 10.0 eq) was added at 0 °C. After complete conversion (TLC-control), the solvent was evaporated *in vacuo*. To a solution of the resulting hydrochloride in dry CH_2Cl_2 (32 mL) Boc-(*S*)-alanine (1.53 g, 8.07 mmol, 1.1 eq), DIPEA (3.90 mL, 22.8 mmol, 3.1 eq) and PyBOP (4.20 g, 8.07 mmol, 1.1 eq) were added successively at 0 °C. After stirring at room temperature overnight, the solvent was evaporated *in vacuo* and the residue was dissolved in EtOAc. The organic layer was washed successsively with 1 M $KHSO_4$-, saturated $NaHCO_3$-, and saturated NaCl-solution. After drying over Na_2SO_4, column chromatography (silica gel, petroleum ether/EtOAc 1:1, 4:6) gave rise to the desired tripeptide **11d** (3.88 g, 6.43 mmol, 88 %) as colorless foam. $[\alpha]_D^{20}$ = +33.9 (c = 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): δ = 0.98 (d, *J* = 6.9 Hz, 3 H), 1.40 (s, 9 H), 2.89 (dd, *J* = 15.2, 11.0 Hz, 1 H), 2.95 (s, 3 H), 3.33 (dd,

J = 15.2, 5.5 Hz, 1 H), 3.72 (s, 3 H), 3.83 (dd, *J* = 17.8, 5.2 Hz, 1 H), 4.13 (dd, *J* = 17.9, 6.5 Hz, 1 H), 4.42 (dq, *J* = 6.8, 6.8 Hz, 1 H), 4.53 (ddd, *J* = 4.8, 1.6, 1.6 Hz, 2 H), 5.22 (d, *J* = 7.0 Hz, 1 H), 5.28 (ddt, *J* = 10.6, 1.4, 1.4 Hz, 1 H), 5.47 (ddt, *J* = 17.3, 1.7, 1.7 Hz, 1 H), 5.54 (dd, *J* = 10.8, 5.6 Hz, 1 H), 6.01 (ddt, *J* = 17.2, 10.5, 4.9 Hz, 1 H), 6.69 (d, *J* = 8.4 Hz, 1 H), 6.93 (dd, *J* = 6.6, 5.4 Hz, 1 H), 7.11 (dd, *J* = 8.4, 2.1 Hz, 1 H), 7.56 (d, *J* = 2.1 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 17.5, 28.3, 30.8, 31.9, 41.0, 46.6, 52.2, 56.7, 69.7, 80.0, 86.4, 112.4, 117.6, 129.7, 131.3, 132.5, 139.4, 155.8, 155.9, 169.9, 170.1, 174.7. HRMS (CI) calcd for $C_{24}H_{35}IN_3O_7^+$ $[M+H]^+$: 604.1514, found: 604.1485.

(*S*)-(*N*-*tert*-Butoxycarbonyl-alanyl)-(*R*)-(*O*-allyl-3-iodo-*N*-methyl-tyrosyl)-glycine-(2*S*,5*E*)-10-(*tert*-butyldimethylsiloxy)-5-methyl-dec-5-en-2-ylester (15dA): Tripeptide **11d** (3.53 g, 5.85 mmol, 1.0 eq) was dissolved in THF/MeOH (3:1, 47 mL) and a solution of LiOH (147 mg, 6.14 mmol, 1.05 eq) in H_2O (12 mL) was added at 0 °C. After complete conversion (TLC-control), the solvent was evaporated *in vacuo* and the residue was acidified with 1 M HCl solution to pH 2. The aqueous layer was extracted with EtOAc, the combined organic layers were dried over Na_2SO_4 and the solvent was evaporated *in vacuo*.

To a solution of the crude acid (1.0 eq) in dry CH_2Cl_2 (47 mL) alcohol **(*S*)-3** (2.11 g, 7.02 mmol, 1.2 eq), DMAP (72 mg, 0.589 mmol, 0.1 eq) and a solution of DCC (1.45 g, 7.02 mmol, 1.2 eq) in dry CH_2Cl_2 (21 mL) were added. After stirring the mixture overnight at room temperature, the solvent was evaporated *in vacuo* and the residue was dissolved in Et_2O. The precipitated urea derivative was filtered off and the solvent was evaporated. Purification by column chromatography (silica gel, petroleum ether/EtOAc 7:3, 6:4, 1:1) gave rise to depsipeptide **15dA** (3.64 g, 4.17 mmol, 71 %) as pale yellow oil. $[\alpha]_D^{20}$ = +18.5 (c = 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.04 (s, 6 H), 0.88 (s, 9 H), 0.97 (d, *J* = 6.8 Hz, 3 H), 1.22 (d, *J* = 6.3 Hz, 3 H), 1.32–1.42 (m, 11 H), 1.50 (m, 2 H), 1.54–1.61 (m, 4 H), 1.66 (m, 1 H), 1.92–2.01 (m, 4 H), 2.88 (dd, *J* = 15.2, 11.1 Hz, 1 H), 2.96 (s, 3 H), 3.33 (dd, *J* = 15.3, 5.5 Hz, 1 H), 3.59 (t, *J* = 6.5 Hz, 2 H), 3.78 (dd, *J* = 18.0, 4.9 Hz, 1 H), 4.13 (dd, *J* = 17.7, 6.6 Hz, 1 H), 4.43 (dq, *J* = 6.8, 6.8 Hz, 1 H), 4.54 (ddd, *J* = 4.6, 1.5, 1.5 Hz, 2 H), 4.91 (m, 1 H), 5.11 (t, *J* = 7.0 Hz, 1 H), 5.23 (d, *J* = 7.0 Hz, 1 H), 5.28 (ddt, *J* = 10.6, 1.4, 1.4 Hz, 1 H), 5.47 (ddt, *J* = 17.3 Hz, 1.6, 1.6 Hz, 1 H), 5.54 (dd, *J* = 10.9, 5.6 Hz, 1 H), 6.01 (ddt, *J* = 17.2, 10.4 Hz, 4.8 Hz, 1 H), 6.69 (d, *J* = 8.5 Hz, 1 H), 6.89 (dd, *J* = 7.0, 4.6 Hz, 1 H), 7.11 (dd, *J* = 8.4, 2.1 Hz, 1 H), 7.56 (d, *J* = 2.1 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = −5.3, 16.0, 17.5, 18.4, 19.9, 26.0, 26.0, 27.6, 28.3, 30.8, 32.0, 32.5, 34.2, 35.3, 41.3, 46.6, 56.7, 63.2, 69.7, 72.3, 79.9, 86.4, 112.3, 117.6, 125.1, 129.7, 131.3, 132.5, 133.9, 139.4, 155.7, 155.9, 169.0, 169.9, 174.7. HRMS (CI) calcd for $C_{35}H_{59}IN_3O_6Si^+$ $[M-Boc+2H]^+$: 772.3212, found: 772.3188.

(*S*)-(*N*-*tert*-Butoxycarbonyl-alanyl)-(*R*)-(*O*-allyl-3-iodo-*N*-methyl-tyrosyl)-glycine-(2*S*,5*E*)-10-hydroxy-5-methyl-dec-5-ene-2-yl ester (16dA): To a solution of silyl-protected depsipeptide **15dA** (3.53 g, 4.05 mmol, 1.0 eq) in dry THF (4.9 mL) a 1 M TBAF-solution in dry THF (4.90 mL, 4.90 mmol, 1.2 eq) was added. After complete deprotection (TLC-control), the reaction mixture was diluted with EtOAc, washed with 1 M HCl- and saturated NaCl-solution and was dried over Na_2SO_4. Purification by column chromatography (silica gel, CH_2Cl_2/Et_2O 7:3) gave rise to alcohol **16dA** (2.58 g, 3.41 mmol, 84 %) as pale yellow oil. $[\alpha]_D^{20}$ = +23.7 (c = 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.94 (d, *J* = 6.9 Hz, 3 H), 1.23 (d, *J* = 6.2 Hz, 3 H), 1.33–1.42 (m, 11 H), 1.49–1.63 (m, 6 H), 1.70 (m, 1 H), 1.97–2.05 (m, 4 H), 2.87 (dd, *J* = 15.2, 11.1 Hz, 1 H), 2.96 (s, 3 H), 3.34 (dd, *J* = 15.2, 5.5 Hz, 1 H), 3.61 (t, *J* = 6.6 Hz, 2 H), 3.73 (dd, *J*= 17.9, 4.9 Hz, 1 H), 4.17 (dd, *J* = 17.9, 6.7 Hz, 1 H), 4.43 (m, 1 H), 4.54 (ddd, *J* = 4.8, 1.6, 1.6 Hz, 2 H), 4.86 (m, 1 H), 5.10 (t, *J* = 6.6 Hz, 1 H), 5.25–5.30 (m, 2 H), 5.47 (ddt, *J* = 17.3, 1.7, 1.7 Hz, 1 H), 5.55 (dd, *J* = 10.9, 5.5 Hz, 1 H), 6.01 (ddt, *J* = 17.2, 10.5, 4.8 Hz, 1 H), 6.69 (d, *J* = 8.4 Hz, 1 H), 7.08–7.12 (m, 2 H), 7.56 (d, *J* = 2.1 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 15.7, 17.6, 20.1, 25.7, 27.4, 28.2, 30.8, 32.1, 32.1, 33.6, 35.5, 41.3, 46.6, 56.7, 62.8, 69.7, 71.9, 80.0, 86.4, 112.4, 117.6, 125.3, 129.8, 131.3, 132.5, 133.8, 139.4, 155.7, 155.9, 169.2, 169.9, 174.6. HRMS (CI) calcd for $C_{34}H_{53}IN_3O_8^+$ $[M+H]^+$: 758.2872, found: 758.2886.

(9*S*,5*E*)-9-((S)-(*N*-*tert*-Butoxycarbonyl-alanyl)-(*R*)-(*O*-allyl-3-iodo-*N*-methyl-tyrosyl)-glycinyl-oxy)-6-methyldec-5-enoic acid (17dA):

Jones-solution (3 M): 1.0 g CrO_3, 2.91 mL H_2O, 0.84 mL H_2SO_4

A 3 M Jones-solution (3.30 mL, 9.90 mmol, 3.0 eq) was added to a solution of alcohol **16dA** (2.51 g, 3.31 mmol, 1.0 eq) in acetone (23 mL). After complete oxidation (TLC-control, 15 min), the reaction was quenched with isopropanol and the solvent was evaporated *in vacuo*. The residue was diluted with H_2O and was extracted with EtOAc. The combined organic layers were washed with saturated NaCl-solution and dried over Na_2SO_4. Purification by column chromatography (silica gel, CH_2Cl_2/Et_2O 9:1, 8:2, 7:3) gave rise to the desired depsipeptide acid **17dA** (1.51 g, 1.96 mmol, 59 %) as colorless foam. $[\alpha]_D^{20}$ = +24.1 (c = 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.87 (d, *J* = 6.9 Hz, 3 H), 1.24 (d, *J* = 6.2 Hz, 3 H), 1.39 (s, 9 H), 1.56 (s, 3 H), 1.60–1.76 (m, 4 H), 1.95–2.09 (m, 4 H), 2.23 (t, *J* = 7.8 Hz, 2 H), 2.85 (dd, *J* = 15.2, 11.6 Hz, 1 H), 2.95 (s, 3 H), 3.42 (dd, *J* = 15.3, 5.3 Hz, 1 H), 3.64 (dd, *J* = 17.8, 4.5 Hz, 1 H), 4.27 (dd, *J* = 17.8, 7.3 Hz, 1 H), 4.53–4.60 (m, 3 H), 4.79 (m, 1 H), 5.04 (t, *J* = 6.8 Hz, 1 H), 5.28 (ddt, *J* = 10.6, 1.5, 1.5 Hz, 1 H), 5.44–5.51 (m, 2 H), 5.63 (dd, *J* = 11.3, 5.3 Hz, 1 H), 6.01 (ddt, *J* = 17.2, 10.6, 4.8 Hz, 1 H), 6.69 (d, *J* = 8.5 Hz, 1 H), 7.11 (dd, *J* = 8.4, 2.2 Hz, 1 H), 7.17 (dd, *J* = 7.1, 4.1 Hz, 1 H), 7.56 (d, *J* = 2.0 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 15.4, 18.0, 20.3, 24.9, 27.0, 28.3, 30.8, 32.3, 33.1, 33.4, 35.6, 41.3, 46.7, 56.8, 69.7, 71.6, 80.3, 86.4, 112.4, 117.6, 124.6, 129.8, 131.4, 132.5, 134.7, 139.5, 155.9, 156.1, 169.4, 170.2, 174.7, 177.0. HRMS (CI) calcd for: $C_{34}H_{51}IN_3O_9^+$ $[M+H]^+$: 772.2664, found: 772.2648.

(6*R*,9*S*,19*S*,15*E*)-6-(4-Allyloxy-3-iodobenzyl)-7,9,16,19-tetramethyl-1-oxa-4,7,10-triazacyclononadec-15-en-2,5,8,11-tetraone (18dA):

EDC·HCl (276 mg, 1.44 mmol, 1.1 eq) was added to a solution of cyclization precursor **17dA** (1.01 g, 1.31 mmol, 1.0 eq) and pentafluorophenol (265 mg, 1.44 mmol, 1.1 eq) in dry CH_2Cl_2 (4.3 mL) at 0 °C. After stirring overnight at room temperature, the mixture was diluted with EtOAc and washed with saturated $NaHCO_3$-solution. After extraction of the aqueous layer, the combined organic layers were dried over Na_2SO_4 and the solvent was evaporated. The obtained crude active ester was diluted with CH_2Cl_2/TFA (4:1, 13 mL). After complete deprotection (TLC-control, 90 min), the reaction mixture was diluted with CH_2Cl_2 (26 mL/mmol) and was slowly added over 75 min to a two-phase-mixture of $CHCl_3$ and saturated $NaHCO_3$-solution (7:1, 525 mL) at 40 °C. After complete addition, the mixture was heated to 60 °C and stirred vigorously overnight. The aqueous layers was extracted with CH_2Cl_2 and the combined organic layers were dried over Na_2SO_4. Purification by column chromatography (silica gel, CH_2Cl_2/Et_2O 7:3, 6:4) gave rise to cyclic depsipeptide **18dA** (501 mg, 0.767 mmol, 59 %) as colorless, shiny foam. $[\alpha]_D^{20}$ = −7.6° (c = 1.0, $CHCl_3$). Melting range: 59–64 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.24 (d, *J* = 6.3 Hz, 3 H), 1.29 (d, *J* = 6.5 Hz, 3 H), 1.50–1.57 (m, 4 H), 1.63–1.86 (m, 3 H), 1.91 (m,1 H), 2.02–2.09 (m, 3 H), 2.19 (m, 2 H), 2.80 (dd, *J* = 14.4, 7.2 Hz, 1 H), 2.91 (s, 3 H), 3.27 (dd, *J* = 14.3, 8.5 Hz, 1 H), 3.40 (dd, *J* = 17.9, 3.3 Hz, 1 H), 4.41 (dd, *J* = 17.9, 9.6 Hz, 1 H), 4.55 (ddd, *J* = 4.7, 1.5, 1.5 Hz, 2 H), 4.82 (dq, *J* = 6.5, 6.5 Hz, 1 H), 4.94 (m, 1 H), 5.05 (t, *J* = 7.0 Hz, 1 H), 5.29 (ddt, *J* = 10.6, 1.5, 1.5 Hz, 1 H), 5.34 (dd, *J* = 8.3, 7.5 Hz, 1 H), 5.49 (ddt, *J* = 17.3, 1.6, 1.6 Hz, 1 H), 6.03 (ddt, *J* = 17.2, 10.4, 4.9 Hz, 1 H), 6.70 (d, *J* = 8.4 Hz, 1 H), 6.75 (dd, *J* = 9.5, 3.1 Hz, 1 H), 6.88 (d, *J* = 7.6 Hz, 1 H), 7.13 (dd, *J* = 8.4, 2.1 Hz, 1 H), 7.62 (d, *J* = 2.1 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 16.2, 17.5, 19.5, 25.7, 26.3, 30.2, 31.3, 33.0, 34.7, 35.0, 40.8, 45.9, 56.5, 69.7, 71.2, 86.7, 112.3, 117.6, 125.4, 129.9, 131.0, 132.5, 134.4, 139.7, 156.0, 169.8, 170.2, 173.1, 173.6, HRMS (CI) calcd for: $C_{29}H_{40}IN_3O_6^+$ $[M]^+$: 653.1956, found: 653.1952.

(6*R*,9*S*,19*S*,*E*)-6-(4-Allyloxy-3-iodo-benzyl)-3-(hydroxy(phenyl)methyl)-7,9,16,19-tetramethyl-1-oxa-4,7,10-triazacyclononadec-15-en-2,5,8,11-tetraon (19dA): Under a nitrogen atmosphere DIPA (0.32 mL, 2.30 mmol, 5.1 eq) was dissolved in dry THF (5.5 mL), cooled to –40 °C before 1.6 M *n*BuLi-solution in hexane (1.4 mL, 2.25 mmol, 5.0 eq) was slowly added. The freshly prepared base solution was stirred for 10 min at room temperature and then cooled to –78 °C. In a second flask macrocycle **18dA** (294 mg, 0.450 mmol, 1.0 eq) was dissolved in dry THF (3.4 mL) and was also cooled to –78 °C. Afterwards the resulting LDA-solution was slowly added to the **18dA** solution to generate a bright red enolate solution. After stirring for 5–10 min at –78 °C, a solution of benzaldehyde (91 µL, 0.900 mmol, 2.0 eq) in dry THF (1.8 mL) was added to the enolate. After complete conversion (TLC-control), the reaction mixture was quenched with 1 M HC solution at –78 °C and was allowed to warm to room temperature. The aqueous layer was extracted with EtOAc and the combined organic layer were dried over Na_2SO_4. Purification by column chromatography (silica gel, petroleum ether/EtOAc 8:2, 7:3, 6:4, 1:1, 4:6, 3:7) gave rise to a diastereomeric mixture of **19dA** (200 mg, 0.263 mmol, 58 %), which could be partially seperated. Three fractions were obtained as colorless foam: diastereomer 1 (45.6 mg, 0.060 mmol, 13 %), diastereomer 2 (95.8 mg (0.126 mmol, 28 %) and diastereomer 3 and 4 (7:3, 58.5 mg (0.077 mmol, 17 %). Additionally a mixed fraction (48.4 mg, 15:85) of educt **18dA** (0.010 mmol, 2 %) and product **19dA** (0.055 mmol, 12 %) was isolated. The diastereomers 1 and 2 were formed in a 7:3 ratio to the diastereomers 3 and 4. Melting range: 65–69 °C. Diastereomer 1: ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.02 (d, *J* = 6.9 Hz, 3 H), 1.30 (d, *J* = 6.1 Hz, 3 H), 1.53 (s, 3 H), 1.63–1.75 (m, 3 H), 1.89–2.22 (m, 5 H), 2.31 (m, 1 H), 2.39–2.45 (m, 4 H), 2.63 (dd, *J* = 15.3, 11.1 Hz, 1 H), 3.33 (dd, *J* = 15.3, 5.7 Hz, 1 H), 4.37 (m, 1 H), 4.52 (ddd, *J* = 4.7, 1.2, 1.2 Hz, 2 H), 4.76 (m, 1 H), 4.98 (t, *J* = 5.0 Hz, 1 H), 5.05 (dd, *J* = 9.4, 2.8 Hz, 1 H), 5.27 (ddt, *J* = 10.6, 1.4, 1.4 Hz, 1 H), 5.46 (ddt, *J* = 17.3, 1.6, 1.6 Hz, 1 H), 5.50–5.58 (m, 3 H), 6.01 (ddt, *J* = 17.2, 10.4, 4.8 Hz, 1 H), 6.10 (d, *J* = 5.0 Hz, 1 H), 6.64 (d, *J* = 8.5 Hz, 1 H), 6.77 (d, *J* = 9.3 Hz, 1 H), 7.03 (dd, *J* = 8.4, 2.0 Hz, 1 H), 7.21 (m, 1 H), 7.30 (m, 2 H), 7.40 (d, *J* = 7.6 Hz, 2 H), 7.46 (d, *J* = 2.0 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 15.2, 16.0, 20.3, 23.1, 27.5, 30.2, 31.6, 33.0, 34.7, 35.3, 46.0, 56.3, 58.7, 69.7, 71.7, 72.8, 86.2, 112.3, 117.6, 124.7, 125.6, 127.1, 128.1, 129.6, 131.4, 132.5, 134.4, 139.2, 140.8, 155.8, 169.4, 170.0, 173.6, 175.4. Diastereomer 2: ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.00 (d, *J* = 6.8 Hz, 3 H), 1.24 (d, *J* = 6.2 Hz, 3 H), 1.51 (s, 3 H), 1.53–1.72 (m, 3 H), 1.83–2.17 (m, 6 H), 2.33–2.41 (m, 4 H), 2.65 (dd, *J* = 15.5, 11.6 Hz, 1 H), 3.36 (dd, *J* = 15.5, 5.3 Hz, 1 H), 4.41 (m, 1 H), 4.52 (ddd, *J* = 4.8, 1.2, 1.2 Hz, 2 H), 4.72 (d, *J* = 3.1 Hz, 1 H), 4.81 (m, 1 H), 4.94 (t, *J* = 6.4 Hz, 1 H), 4.97 (dd, *J* = 8.2, 6.6 Hz, 1 H), 5.25–5.29 (m, 2 H), 5.45 (ddt, *J* = 17.2, 1.6, 1.6 Hz, 1 H), 5.55 (dd, *J* = 11.5, 5.3 Hz, 1 H), 5.95–6.05 (m, 2 H), 6.65 (d, *J* = 8.4 Hz, 1 H), 7.05 (dd, *J* = 8.4, 2.0 Hz, 1 H), 7.16 (d, *J* = 8.4 Hz, 1 H), 7.25 (m, 1 H), 7.32 (m, 2 H), 7.39 (d, *J* = 7.1 Hz, 2 H), 7.47 (d, *J* = 2.0 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 15.3, 16.4, 20.1, 23.6, 27.5, 30.1, 31.6, 32.9, 34.8, 35.7, 45.6, 56.3, 57.8, 69.7, 71.6, 74.2, 86.3, 112.3, 117.6, 125.3, 127.2, 128.0, 128.2, 129.5, 131.3, 132.5, 133.9, 139.1, 139.7, 155.8, 169.7, 170.3, 174.0, 174.2. Diastereomeres 3 und 4: ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.09 (d, *J* = 6.3 Hz, 1.0 H), 1.17 (d, *J* = 6.5 Hz, 1.0 H), 1.25 (d, *J* = 6.4 Hz, 2.0 H), 1.26 (d, *J* = 6.2 Hz, 2.0 H), 1.53 (s, 1.0 H), 1.55 (s, 2.0 H), 1.57–2.26 (m, 10 H), 2.70 (dd, *J* = 14.7, 8.1 Hz, 0.7 H), 2.76–2.81 (m, 3.3 H), 3.03 (dd, *J* = 14.7, 7.8 Hz, 0.7 H), 3.14 (dd, *J* = 14.7, 7.7 Hz, 0.3 H), 3.63 (d, *J* = 2.7, 0.7 H), 3.75 (d, *J* = 4.8 Hz, 0.3 H), 4.54 (m, 2.0 H), 4.62 (dd, *J* = 9.4, 1.8 Hz, 0.7 H), 4.72–4.84 (m, 1.6 H,), 4.94–5.04 (m, 1.0 H), 5.09 (t, *J* = 6.8 Hz, 0.7 H), 5.14 (dd, *J* = 4.9, 3.5 Hz, 0.3 H), 5.25–5.36 (m, 2.7 H), 5.49 (m, 1.0 H), 6.03 (m, 1 H), 6.45 (d, *J* = 7.9 Hz, 0.3 H), 6.58 (d, *J* = 8.5 Hz, 0.7 H), 6.68 (d, *J* = 8.5 Hz, 0.3 H), 6.83 (d, *J* = 7.9 Hz, 0.7 H), 6.91 (dd, *J* = 8.4, 2.0 Hz, 0.4 H), 7.02 (d, *J* = 8.7 Hz, 0.3 H), 7.05–7.07 (m, 1.0 H), 7.25–7.36 (m, 5 H), 7.46 (d, *J* = 2.0 Hz, 0.7 H), 7.55 (d, *J* = 2.0 Hz, 0.3 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 15.9, 16.1, 17.5, 17.7, 19.2, 19.9, 25.2, 25.7, 26.2, 26.4, 30.0, 30.1, 30.8, 31.1, 32.7, 32.7, 34.8, 34.8, 34.9, 45.4, 45.7, 56.0, 56.1, 57.9, 58.4, 69.7, 69.7, 71.0, 71.8, 72.9, 73.6, 86.5, 86.6, 112.2, 112.3, 117.5, 117.6, 125.2, 125.6, 125.7, 126.1, 128.0, 128.0, 128.2, 128.3, 129.6, 129.8, 130.8, 130.9, 132.5, 132.5, 134.0, 134.4, 139.1, 139.4, 139.5, 140.1, 155.8, 156.0, 169.3, 169.6, 169.8, 170.0, 172.9, 173.2, 173.5, 173.5. HRMS (CI) calcd for: $C_{36}H_{46}IN_3O_7^+$ [M]$^+$: 759.2375, found: 759.2364. Elemental analysis calcd for $C_{36}H_{46}IN_3O_7$ (757.65): C 56.92, H 6.10, N 5.53, found: C 56.92, H 5.91, N 5.34.

(6*R*,9*S*,19*S*,*E*)-6-(4-Allyloxy-3-iodo-benzyl)-3-benzoyl-7,9,16,19-tetra-methyl-1-oxa-4,7,10-tri-azacyclononadec-15-en-2,5,8,11-tetraon (20dA): The aldol product **19dA** (183 mg, 241 µmol, 1.0 eq) was dissolved in dry CH_2Cl_2 (4.8 mL) and Dess Martin periodinane (123 mg, 289 µmol, 1.2 eq) was slowly added at room temperature. After complete oxidation (TLC-control, 75 min), the reaction mixture was diluted with Et_2O, washed with a mixture of 1 M NaOH- and saturated $Na_2S_2O_3$- as well as saturated NaCl-solution. The aqueous layer was extracted with EtOAc and the combined organic layers were dried over Na_2SO_4. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography (silica gel, CH_2Cl_2/Et_2O 9:1, 8:2). The desired ketone **20dA** (149 mg, 197 µmol, 82 %) was obtained as colorless foam. The diastereomers were formed in a 94:6 ratio (in $CDCl_3$). $[\alpha]_D^{20}$ = +8.7 (c = 1.0, $CHCl_3$). Melting range: 60–65 °C. Major Diastereomer: ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.19 (d, *J* = 6.3 Hz, 3 H), 1.32 (d, *J* = 6.5 Hz, 3 H), 1.35–1.53 (m, 6 H), 1.61–1.72 (m, 3 H), 1.98 (m, 2 H), 2.18 (m, 2 H), 2.83 (dd, *J* = 14.4, 7.4 Hz, 1 H), 2.96 (s, 3 H), 3.26 (dd, *J* = 14.4, 8.4 Hz, 1 H), 4.54 (ddd, *J* = 4.8, 1.1, 1.1 Hz, 2 H), 4.80 (t, *J* = 7.3 Hz, 1 H), 4.85 (m, 1 H), 4.97 (dq, *J* = 8.5, 6.5 Hz, 1 H), 5.28 (ddt, *J* = 10.8, 1.5, 1.5 Hz, 1 H), 5.40–5.50 (m, 2 H, 5-H), 6.02 (ddt, *J* = 17.1, 10.5, 4.8 Hz, 1 H), 6.11 (d, *J* = 8.6 Hz, 1 H), 6.53 (d, *J* = 8.3 Hz, 1 H), 6.68 (d, *J* = 8.5 Hz, 1 H), 7.12 (dd, *J* = 8.4, 2.1 Hz, 1 H), 7.46–7.52 (m, 3 H), 7.62–7.66 (m, 2 H), 8.06 (d, *J* = 7.3 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 15.5, 18.0, 20.0, 25.8, 26.5, 30.3, 31.2, 32.4, 34.5, 35.3, 45.3, 56.2, 57.6, 69.7, 72.0, 86.6, 112.4, 117.6, 125.7, 128.8, 129.7, 129.8, 131.0, 132.5, 133.7, 134.0, 134.6, 139.8, 156.0, 166.2, 169.5, 172.9, 174.1, 191.0. Minor diastereomer (selected signals): ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.09 (d, *J* = 6.8 Hz, 3 H), 1.17 (d, *J* = 6.4 Hz, 3 H), 2.95 (s, 3 H), 3.32 (dd, *J* = 15.4, 6.2 Hz, 1 H), 4.48 (ddd, *J* = 5.4, 1.6, 1.6 Hz, 2 H), 5.09 (t, *J* = 6.8 Hz, 1 H), 5.38 (ddt, *J* = 17.3, 1.5, 1.5 Hz, 1 H), 5.60 (dd, *J* = 10.4, 6.2 Hz, 1 H), 5.94 (d, *J* = 6.8 Hz, 1 H), 6.36 (d, *J* = 7.1 Hz, 1 H), 6.80 (d, *J* = 8.7 Hz, 1 H), 7.09 (dd, *J* = 8.5, 2.2 Hz, 1 H). The ^{13}C signals of the minor diastereomer are not visible in the background noise of the spectrum. LC-MS: *Luna*, 0.6 mL/min, 254 nm, ACN/H_2O 7:3 t_R = 2.98, 3.61 min. HRMS (CI) calcd for: $C_{36}H_{45}IN_3O_7^+$ [M+H]$^+$: 758.2297, found: 758.2269. Elemental analysis calcd for $C_{36}H_{44}IN_3O_7$ (757.65): C 57.07, H 5.85, N 5.55, found: C 57.27, H 5.73, N 5.40.

(6*R*,9*S*,19*S*,*E*)-3-Benzoyl-6-(3-iodo-4-hydroxybenzyl)-7,9,16,19-tetra-methyl-1-oxa-4,7,10-triaza-cyclononadec-15-en-2,5,8,11-tetraon (22dA): The protected ketone **20dA** (50 mg, 66.0 µmol, 1.0 eq) was dissolved in dry MeOH (1.0 mL). Quinaldic acid (1.1 mg, 6.6 µmol, 0.1 eq) as well as Ru-catalyst (2.9 mg, 6.6 µmol, 0.1 eq) were added at room temperature. After complete deprotection (LC-MS-control, 1 h 45 min), DMSO (23 µL, 330 µmol) was added and stirred overnight. The solvent was evaporated *in vacuo* and purified by column chromatography (silica gel, CH_2Cl_2/Et_2O 95:5, 9:1, 8:2, 7:3). Deprotected ketone **22dA** (44.8 mg, 62.4 µmol, 95 %) was obtained as colorless solid. The diastereomers were formed in a 94:6 ratio (in $CDCl_3$). Major diastereomer: ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.18 (d, *J* = 6.3 Hz, 3 H), 1.30 (d, *J* = 6.5 Hz, 3 H), 1.34–1.49 (m, 5 H), 1.60–1.67 (m, 3 H), 1.98 (m, 2 H), 2.19 (m, 2 H), 2.82 (dd, *J* = 14.4, 7.5 Hz, 1 H), 2.96 (s, 3 H), 3.24 (dd, *J* = 14.4, 8.3 Hz, 1 H), 4.78 (t, *J* = 7.1 Hz, 1 H), 4.83 (m, 1 H), 4.97 (m, 1 H), 5.45 (dd, *J* = 8.0, 7.3 Hz, 1 H), 6.10 (d, *J* = 8.5 Hz, 1 H), 6.53 (bs, 1 H), 6.59 (d, *J* = 8.3 Hz, 1 H), 6.84 (d, *J* = 8.3 Hz, 1 H), 7.06 (dd, *J* = 8.3, 1.9 Hz, 1 H), 7.48–7.51 (m, 4 H), 7.63 (m, 1 H), 8.06 (d, *J* = 7.5 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 15.5, 17.9, 20.0, 25.8, 26.5, 30.4, 31.2, 32.3, 34.5, 35.3, 45.3, 56.3, 57.6, 72.0, 85.2, 115.0, 125.7, 128.8, 129.7, 130.3, 130.5, 133.7, 134.0, 134.7, 138.6, 154.2, 166.1,

169.5, 173.2, 174.1, 191.0. Minor diastereomer (selected signals): ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.03 (d, *J* = 6.8 Hz, 3 H), 1.17 (d, *J* = 6.4 Hz, 3 H), 2.38 (m, 2 H), 3.33 (dd, *J* = 15.2, 6.5 Hz, 1 H), 5.06 (t, *J* = 7.1 Hz, 1 H), 5.61 (dd, *J* = 10.5, 6.0 Hz, 1 H), 5.98 (d, *J* = 7.0 Hz, 1 H), 6.47 (d, *J* = 7.0 Hz, 1 H), 7.02 (dd, *J* = 8.5, 1.9 Hz, 1 H), 7.59 (m, 1 H), 8.00 (d, *J* = 7.4 Hz, 2 H). The ^{13}C signals of the minor diastereomer are not visible in the background noise of the spectrum. LC-MS: *Luna*, 0.6 mL/min, 254 nm, ACN/H_2O 7:3, t_R = 2.24, 2.67 min. HRMS (CI) calcd for: $C_{33}H_{40}IN_3O_7^+$ $[M+H]^+$: 717.1905, found: 717.1871.

(6*R*,9*S*,19*S*,15*E*)-6-(4-Allyloxy-3-bromo-benzyl)-3-((7-(diethylamino)-2-oxo-2*H*-chrom-en-4-yl)(hydroxy)methyl)-7,9,16,19-tetramethyl-1-oxa-4,7,10-triazacyclonona-dec-15-en-2,5,8, 11-tetraon (27cA): Under a nitrogen atmosphere DIPA (0.13 mL, 928 µmol) was dissolved in dry THF (1.4 mL), cooled to –40 °C before 1.6 M *n*BuLi-solution in hexane (0.55 mL, 875 µmol) was slowly added. The freshly prepared base solution was stirred for 10 min at room temperature and then cooled to –78 °C. In a second flask dried zinc chloride (31.1 mg, 228 µmol) and macrocycle **18cA**[19] (106 mg, 175 µmol) were dissolved in dry THF (1.7 mL), also cooled to –78 °C and slowly added to the freshly prepared LDA-solution. After stirring the bright red enolate solution for 30 min at –78 °C for transmetallation, a solution of 7-(diethylamino)-2-oxo-2*H*-chromen-4-carbaldehyde[41c] (64.5 mg, 263 µmol) in dry THF (0.5 mL) was added. After complete conversion (TLC-control), the reaction mixture was diluted with Et_2O, hydrolyzed with 1 M NH_4Cl-solution and allowed to warm up to room temperature. The aqueous layer was extracted with EtOAc and the combined organic layers were dried over Na_2SO_4. After evaporation of the solvent, the residue was separated by preparative HPLC (RP, *Reprosil*, ACN/H_2O 7:3) in two fractions. Aldol product **27cA** (56.8 mg, 66.7 µmol, 38 %) was obtained as a yellow solid and the corresponding vinyl ether (6.0 mg, 7.0 µmol, 4 %) was isolated. Since the signals of two diastereomers are overlapping in the NMR-spectrum, there are three sets of signals in a 6:2:2 ratio. Mixture of diastereomers: ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.02 (d, *J* = 6.3 Hz, 1.8 H), 1.08 (d, *J* = 6.9 Hz, 0.6 H), 1.16–1.25 (m, 9 H), 1.33 (d, *J* = 6.3 Hz, 0.6 H), 1.43 (m, 0.6 H), 1.48 (s, 0.6 H), 1.56 (s, 2.4 H), 1.59–1.86 (m, 3.4 H), 1.88–2.36 (m, 6 H), 2.75–2.95 (m, 4 H), 3.07 (dd, *J* = 15.2, 7.0 Hz, 0.3 H), 3.27 (dd, *J* = 15.0, 6.9 Hz, 0.7 H), 3.33–3.43 (m, 4 H), 4.25 (d, *J* = 4.1 Hz, 0.5 H), 4.41 (d, *J* = 3.0 Hz, 0.2 H), 4.55–4.59 (m, 2.2 H), 4.75–4.94 (m, 2.5 H), 5.00–5.14 (m, 1.3 H), 5.26–5.31 (m, 2.1 H), 5.37–5.52 (m, 1.8 H), 5.61 (dd, *J* = 11.1, 5.6 Hz, 0.2 H), 5.70 (m, 0.2 H), 6.03 (m, 1.0 H), 6.28 (d, *J* = 0.9 Hz, 0.6 H), 6.35–6.37 (m, 0.6 H), 6.44 (d, *J* = 2.5 Hz, 0.2 H), 6.50 (d, *J* = 2.5 Hz, 0.8 H), 6.58 (dd, *J* = 9.1, 2.5 Hz, 0.2 H), 6.66 (dd, *J* = 9.1, 2.6 Hz, 0.8 H), 6.75–6.83 (m, 1.8 H), 6.95 (dd, *J* = 8.5, 2.1 Hz, 0.2 H), 7.05 (dd, *J* = 8.4, 2.2 Hz, 0.8 H), 7.09 (d, *J* = 9.6 Hz, 0.3 H), 7.26 (m, 0.2 H), 7.32 (d, *J* = 2.1 Hz, 0.2 H), 7.34 (d, *J* = 2.1 Hz, 0.6 H), 7.38–7.40 (m, 0.4 H), 7.46 (d, *J* = 8.7 Hz, 0.5 H), 7.58 (d, *J* = 9.1 Hz, 0.6 H), 7.82 (d, *J* = 9.1 Hz, 0.2 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 12.5, 15.3, 15.8, 16.2, 16.3, 17.7, 17.7, 19.0, 20.0, 20.2, 23.6, 25.3, 25.6, 26.3, 26.4, 27.0, 30.2, 30.2, 30.6, 30.9, 31.2, 32.7, 32.8, 31.1, 34.8, 34.8, 35.0, 35.2, 44.7, 45.4, 45.6, 46.1, 53.4, 55.7, 55.8, 56.2, 56.3, 56.7, 68.4, 69.6, 69.7, 70.5, 70.9, 71.5, 72.2, 72.5, 97.8, 97.9, 98.0, 105.4, 105.9, 106.2, 106.8, 108.0, 108.8, 109.0, 111.9, 112.0, 112.2, 113.6, 113.7, 117.6, 117.7, 117.8, 123.8, 124.7, 125.1, 125.2, 125.3, 125.9, 128.0, 128.5, 130.1, 130.3, 130.5, 132.5, 132.7, 133.1 133.4, 133.5, 133.8, 134.2, 134.6, 150.3, 150.4, 150.6, 153.5, 153.6, 153.7, 153.8, 154.0, 154.3, 156.2, 156.4, 162.3, 162.4, 162.5, 167.7, 168.2, 169.2, 169.6, 169.9, 170.0, 173.1, 173.3, 174.0, 174.2, 174.6, 175.0. LC-MS: *Luna*, 0.6 mL/min, 254 nm, ACN/H_2O 7:3, t_R = 5.11 min. HRMS (CI) calcd for: $C_{43}H_{55}BrN_4O_9^+$ $[M]^+$: 850.3147, found: 850.3158.

(6*R*,9*S*,19*S*,15*E*)-6-(3-Bromo-4-hydroxybenzyl)-7,9,16,19-tetramethyl-1-oxa-4,7,10-triazacyclono-nadec-15-en-2,5,8,11-tetraon (29cA): To the allyl ether **18cA**[19] (40.0 mg, 66.0 µmol, 1.0 eq) dissolved in dry MeOH (1.0 mL) quinaldic acid (1.1 mg, 6.60 µmol, 0.1 eq) as well as Ru-catalyst (2.9 mg, 6.60 µmol, 0.1 eq) were added at room temperature. After complete deprotection (LC-MS-control, 2 h), DMSO (23 µl, 330 µmol) was added and stirred over night. The solvent was evaporated *in vacuo* and purified by column chromatography (silica gel, CH_2Cl_2/Et_2O 7:3). Deprotected cyclopeptide **29cA** (36.6 mg, 64.6 µmol, 98 %) was obtained as colorless solid. $[\alpha]_D^{20}$ = +2.7 (c = 1.00, $CHCl_3$). Melting range: 75–79 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.23 (d, *J* = 6.3 Hz, 3 H), 1.28 (d, *J* = 6.5 Hz, 3 H), 1.50–1.56 (m, 4 H), 1.62–1.84 (m, 3 H), 1.90 (m, 1 H), 2.01–2.10 (m, 3 H), 2.19 (m, 2 H), 2.80 (dd, *J* = 14.4, 7.2 Hz, 1 H), 2.91 (s, 3 H), 3.28 (dd, *J* = 14.3, 8.5 Hz, 1 H), 3.40 (dd, *J* = 17.9, 3.2 Hz, 1 H), 4.40 (dd, *J* = 17.9, 9.6 Hz, 1 H), 4.82 (m, 1 H), 4.93 (m, 1 H), 5.04 (t, *J* = 6.9 Hz, 1 H), 5.33 (dd, *J* = 8.7, 7.1 Hz, 1 H), 6.29 (bs, 1 H), 6.77 (dd, *J* = 9.5, 3.0 Hz, 1 H), 6.90 (d, *J* = 8.4 Hz, 1 H), 6.92 (d, *J* = 7.9 Hz, 1 H), 7.04 (dd, *J* = 8.3, 1.9 Hz, 1 H), 7.30 (d, *J* = 1.8 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 16.2, 17.4, 19.6, 25.7, 26.2, 30.2, 31.5, 32.9, 34.7, 35.0, 40.8, 45.9, 56.6, 71.3, 110.1, 116.2, 125.3, 129.5, 130.0, 132.4, 134.4, 151.4, 169.8, 170.2, 173.3, 173.6. LC-MS: *Luna*, 0.6 mL/min, 254 nm, ACN/H_2O 7:3, t_R = 1.44 min. HRMS (CI) calcd for: $C_{26}H_{38}BrN_3O_6^+$ $[M+2H]^+$: 567.1938, found: 567.1955.

(6*R*,9*S*,19*S*,15*E*)-6-(3-Iodo-4-hydroxybenzyl)-7,9,16,19-tetramethyl-1-oxa-4,7,10-triaza-cyclononadec-15-en-2,5,8,11-tetraon (29dA): To the allyl ether **18dA** (35.0 mg, 53.6 µmol, 1.0 eq) dissolved in dry MeOH (0.8 mL) quinaldic acid (1.0 mg, 5.90 µmol, 0.11 eq) as well as Ru-catalyst (2.3 mg, 5.36 µmol, 0.1 eq) were added at room temperature. After complete deprotection (LC-MS-control, 1 h), DMSO (19 µl, 268 µmol) was added and stirred over night. The solvent was evaporated *in vacuo* and purified by column chromatography (silica gel, CH_2Cl_2/Et_2O 6:4, 1:1). Deprotected cyclopeptide **29dA** (32.9 mg, 53.6 µmol, 99 %) was obtained as colorless solid. $[\alpha]_D^{20}$ = –10.2 (c = 1.00, $CHCl_3$). Melting range: 79–83 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.23 (d, *J* = 6.3 Hz, 3 H), 1.27 (d, *J* = 6.5 Hz, 3 H), 1.50–1.56 (m, 4 H), 1.63–1.84 (m, 3 H), 1.91 (m,1 H), 2.01–2.10 (m, 3 H), 2.20 (m, 2 H), 2.80 (dd, *J* = 14.4, 7.4 Hz, 1 H), 2.91 (s, 3 H), 3.26 (dd, *J* = 14.4, 8.4 Hz, 1 H), 3.42 (dd, *J* = 17.9, 3.3 Hz, 1 H), 4.40 (dd, *J* = 17.9, 9.5 Hz, 1 H), 4.81 (dq, *J* = 6.5, 6.5 Hz, 1 H), 4.93 (m, 1 H), 5.05 (t, *J* = 6.9 Hz, 1 H), 5.34 (dd, *J* = 8.5, 7.3 Hz, 1 H), 6.52 (s, 1 H), 6.78 (dd, *J* = 9.5, 3.2 Hz, 1 H), 6.86 (d, *J* = 8.3 Hz, 1 H), 6.91 (d, *J* = 7.6 Hz, 1 H), 7.06 (dd, *J* = 8.3, 2.0 Hz, 1 H), 7.50 (d, *J* = 2.0 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 16.2, 17.4, 19.6, 25.6, 26.2, 30.3, 31.3, 33.0, 34.7, 35.0, 40.8, 45.9, 56.6, 71.3, 85.2, 115.1, 125.3, 130.4, 130.5, 134.4, 138.6, 154.2, 169.8, 170.1, 173.4, 173.6. LC-MS: *Luna*, 0.6 mL/min, 254 nm, ACN/H_2O 7:3, t_R = 1.50 min. HRMS (CI) calcd for: $C_{26}H_{36}IN_3O_6^+$ $[M]^+$: 613.1643, found: 613.1645.

Experimental procedures, spectroscopic data, and copies of ^{1}H and ^{13}C NMR spectra are available in the Supporting Information.

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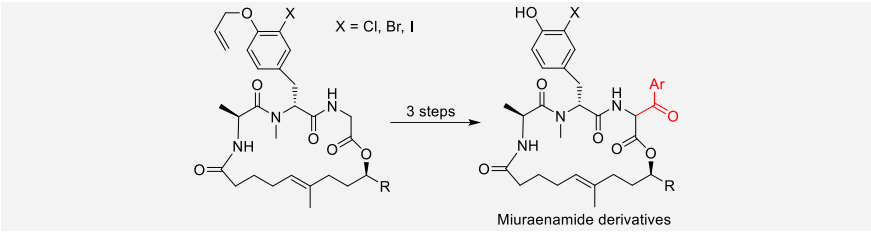
Natural product modification



Late stage peptide modification allows the synthesis of a library of (simplified) miuraenamide derivatives with different halogenation and substitution pattern.

SAR studies indicate, that bromination of the central tyrosine is essential for good biological activity, while the *C*-terminal side chain can be removed.

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Synthesis and biological evaluation of (modified) miuraenamides

Keywords: actin, cyclodepsipeptides, late stage modifications, natural products, peptide modifications