Natural Product Synthesis

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Total Syntheses and Biological Evaluation of Miuraenamides**

*Lisa Karmann, Katharina Schultz, Jennifer Herrmann, Rolf Müller, and Uli Kazmaier**

Abstract: *The miuraenamides, relatively simple representatives of a class of cyclodepsipeptides with high antitumor activity, can be easily and flexibly obtained by the concept of peptide modification. A reaction sequence consisting of an aldol reaction, oxidation, and methylation of the glycine subunit of the cyclodepsipeptides allows the incorporation of the unusual α,β-unsaturated dehydroamino acid in one of the last steps of the synthesis.*

Because of their interesting biological activities, cyclic peptides and depsipeptides are excellent candidates for drug development.[1] Many of these natural products are isolated from marine or terrestrial (micro)organisms. The cyclodepsipeptides of the jasplakinolide type are an especially interesting group. Jasplakinolide (jaspamide)[2] and the structurally closely related geodiamolides[3] were isolated in the 1980s from sponges and found to be highly cytotoxic metabolites (Figure 1). Owing to their interesting biological activities, the first total syntheses of these compounds were published shortly thereafter.[4] For jasplakinolide, in particular, a series of very nice syntheses have been developed in the meanwhile, which were covered in a recent review.[5] By far the most biological studies have also been carried out with this natural product. Most biological effects can be explained by a stabilization of the actin skeleton,[6] which induces apoptosis in a wide range of tumor cell lines.[7] The situation is very similar for the geodiamolides.[8]

In 1995, Höfle and Reichenbach reported the isolation of the chondramides, which are structurally closely related compounds.[9] These compounds have also been successfully synthesized in the meanwhile, and their biological activities have been investigated.[10] Like the two other compound classes, the chondramides also bind to actin.[11]

Interestingly, the chondramides are not produced by sponges, but by myxobacteria. Although myxobacteria had been presumed to be terrestrial microorganisms for a long time, a few marine myxobacteria could be isolated and characterized during the last years.[12] For example, a halophilic myxobacterium of the species *Paraliomyxa miuraensis* SMH-27-4 was isolated from soil samples of the Japanese coast; these myxobacteria produce halogen-containing miuraenamides, cyclodepsipeptides that are closely related to the previously mentioned representatives.[13] The miuraenamides show antimicrobial activity and inhibit NADH oxidase. First studies have also indicated that the miuraenamides also stabilize actin filaments,[14] which is not really surprising in light of their closely related structure.

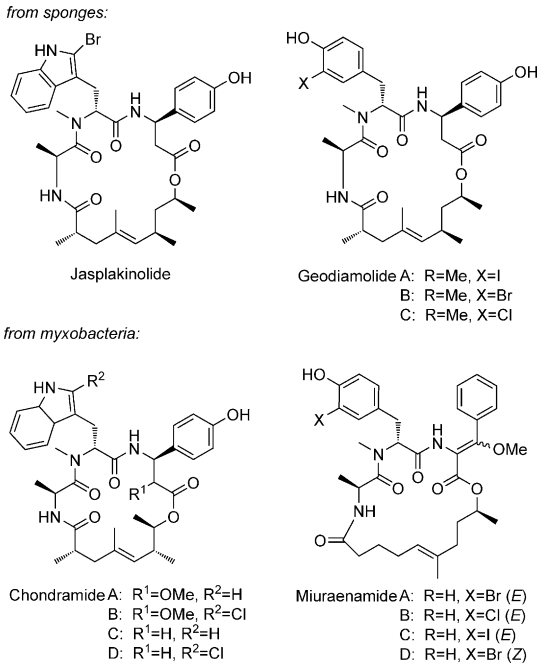

Figure 1. Cyclodepsipeptides of the jasplakinolide type.

Biosynthetically, the cyclodepsipeptides are produced by multienzyme complexes that contain polyketide synthetases (PKS) as well as nonribosomal peptide synthetases (NRPS).[1d,15] The "polyketide fragments" of jasplakinolide and geodiamolide are identical, varying slightly from those of the chondramides and miuraenamides, whereas the latter incorporate the simplest hydroxycarboxylic acid by far. The tripeptide fragment also seems to be rather conserved, especially at the N terminus. Adjacent to the N-terminal alanine, an N-methylated halogenated aromatic amino acid is incorporated. The greatest difference is found at the C terminus of the miuraenamides, where an aromatic β-methoxyacrylate unit is incorporated instead of β-tyrosine. This structural motif is a known pharmacophore of fungicides, addressing the mitochondrial cytochrome bc_1. This unit is probably responsible for the antimicrobial activity,[13b,16] but its influence on actin binding is still unclear. Miuraenamide E

[*] L. Karmann, Dr. K. Schultz, Prof. Dr. U. Kazmaier
Institute for Organic Chemistry, Saarland University
P.O. box 151150, 66041 Saarbrücken (Germany)
E-mail: u.kazmaier@mx.uni-saarland.de
Homepage: http://www.uni-saarland.de/lehrstuhl/kazmaier
Dr. J. Herrmann, Prof. Dr. R. Müller
Helmholtz Institute for Pharmaceutical Research Saarland (HIPS)
and Institute of Pharmaceutical Biotechnology
Saarland University Campus, Building C2.3
66123 Saarbrücken (Germany)

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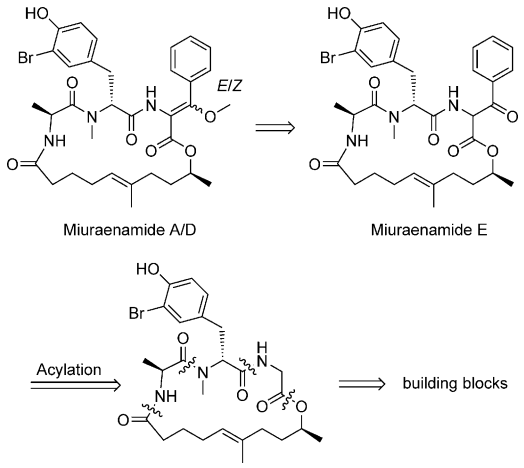


Scheme 1. Retrosynthetic analysis of the miuraenamides.

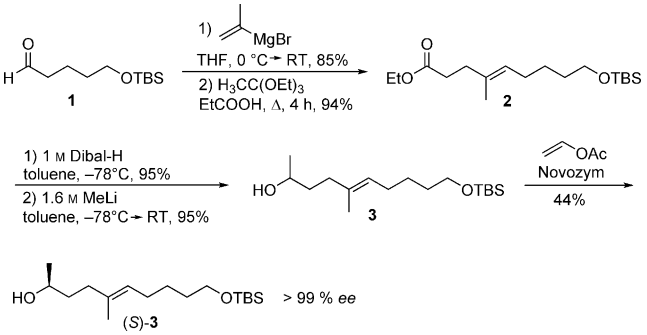
(Scheme 1), which is also naturally occurring and contains a β-keto functional group, might be a hydrolysis product of miuraenamide A and/or D or a biosynthetic precursor of these two compounds, as the biosynthetic pathway of miuraenamide formation has not been elucidated thus far. We thus assumed that the C-terminal position of the tripeptide fragment might be the best position for modifications.

For a couple of years, our group has been involved in the synthesis of myxobacterial natural products and derivatives thereof.[17] Therefore, we were interested in developing a synthetic protocol towards the miuraenamides that allows the introduction of the C-terminal amino acid side chain at a very late stage of the synthesis. Our goal was the introduction of the benzoyl group by acylation of the corresponding glycine peptide, preferentially in the last step. C-Benzoylation would directly lead to miuraenamide E, which can be converted into miuraenamide A/D by O-methylation (Scheme 1). Macrolactamization should generate the required peptide ring, and the linear precursor is easily available from the corresponding building blocks. This method would allow the easy generation of libraries of miuraenamide derivatives for structure–activity relationship (SAR) studies.

This kind of peptide modification was first reported by Seebach et al. in the early 1990s, who showed that peptides can be deprotonated and alkylated regioselectively at sarcosine subunits using an excess of LDA.[18] The regio- and stereoselective alkylation of cyclosporine was definitely the most spectacular example.[19]

Our group has also studied peptide modifications that involve peptide metal complexes for a couple of years.[20] By far the best results were obtained with transition-metal-catalyzed allylic alkylations;[21] these reactions allow the stereoselective introduction of unsaturated side chains into peptides, which can subsequently be subjected to further modifications.[22] This approach is suitable for modifications of C-terminal glycine ester enolates[23] as well as internal glycine amide units.[24] Therefore, the miuraenamides, with their exotic amino acids at the C terminus, are particularly suitable synthetic targets for the peptide modification approach.

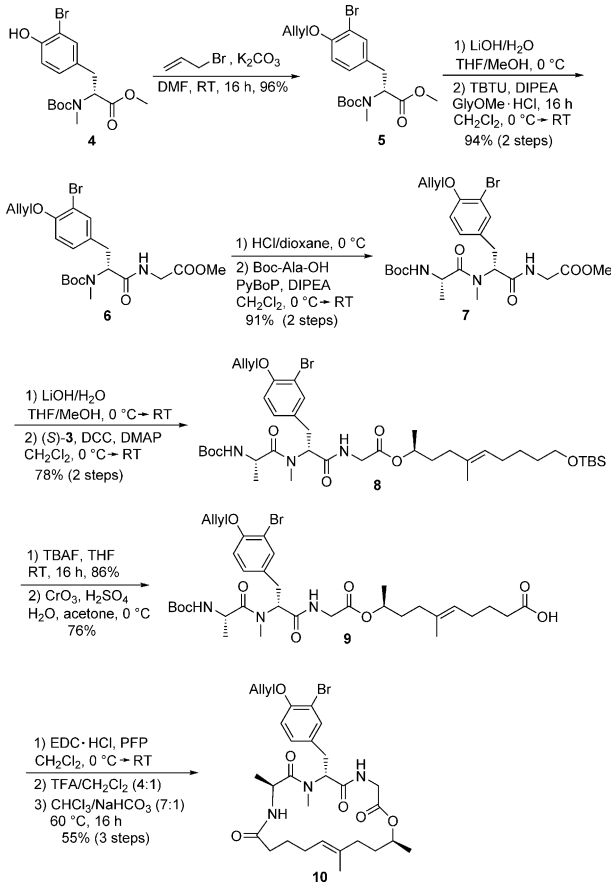
The Johnson–Claisen rearrangement[25] was chosen as the key step of the synthesis of the required unsaturated hydroxycarboxylic acid. Starting from the known silyl-protected aldehyde **1**,[26] the addition of isopropenylmagnesium bromide generated the corresponding allylic alcohol, which could be subjected to the reaction conditions of the Johnson–Claisen rearrangement (Scheme 2). The *E*-configured γ,δ-



Scheme 2. Synthesis of hydroxycarboxylic acid precursor (*S*)-**3**. Dibal-H = diisobutylaluminum hydride, TBS = *tert*-butyldimethylsilyl.

unsaturated ester **2** was obtained stereoselectively in excellent yield. Reduction with Dibal-H generated the corresponding aldehyde, which had to be purified by flash column chromatography as the crude product was contaminated by traces of the primary alcohol, which resulted from over-reduction. Subsequent addition of MeLi gave rise to alcohol **3**, which was subjected to an enzymatic kinetic resolution using Novozym 435. The *R* alcohol was acetylated selectively, and the required *S* alcohol could be isolated in enantiomerically pure form.

The synthesis of the tripeptide fragment started from the known brominated tyrosine derivative **4** (Scheme 3).[27] To suppress side reactions on the aromatic ring, the phenolic hydroxy group was protected as its allyl ether (**5**). Subsequent saponification and coupling with methyl glycinate gave rise to dipeptide **6** in high yield. Removal of the Boc protecting group and coupling with Boc-protected alanine using PyBOP[28] as the coupling reagent generated the desired tripeptide **7**. Saponification and Steglich esterification[29] using (*S*)-**3** provided linear precursor **8**. The primary alcohol was obtained by desilylation, but the subsequent oxidation, which should provide the required carboxylic acid **9**, was not trivial. A range of different oxidation reagents, such as CrO_3/pyridine, PDC, TEMPO, or the Dess–Martin periodinane in combination with a subsequent Lindgren oxidation, failed to yield the desired product because of side reactions, for example, at the double bond. Finally, Jones oxidation using CrO_3 under acidic conditions provided the desired acid **9** in acceptable yield.[30] However, the reaction must be quenched after a short period of time to avoid significant side reactions such as removal of the Boc protecting group. For the macrolactamization, we chose Schmidt's pentafluorophenyl ester method.[31]

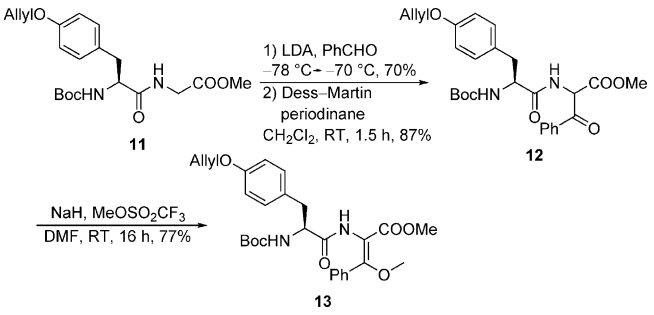


Scheme 3. Synthesis of miuraenamide precursor **10**. Boc = *tert*-butoxycarbonyl, DCC = 1,3-dicyclohexylcarbodiimide, DIPEA = diisopropylethylamine, DMAP = 4-dimethylaminopyridine, EDC = 3-(3-dimethylaminopropyl)-1-ethylcarbodiimide, PFP = pentafluorophenol, PyBoP = (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate, TBAF = tetrabutylammonium fluoride, TBTU = *O*-benzotriazol-1-yl-*N*-tetramethyluronium tetrafluoroborate, TFA = trifluoroacetic acid.

The pentafluorophenyl ester was obtained by coupling of the corresponding acid with pentafluorophenol in the presence of EDC; its Boc protecting group was directly removed with trifluoroacetic acid without prior purification. The corresponding trifluoroacetate could not be isolated by solvent evaporation, as under these conditions, side reactions of the acid-labile trisubstituted double bond were observed. The whole reaction mixture was thus diluted with CH_2Cl_2 and directly added dropwise to a stirred suspension of $CHCl_3$ and sat. $NaHCO_3$ solution at 40 °C. Stirring was continued overnight at 60 °C, and the desired macrocycle **10** could be obtained in 55% yield over three steps.

Building block **10** is the ideal candidate for the synthesis of miuraenamide derivatives by modifications of the glycine units. For the natural products themselves, C-benzoylation and subsequent O-methylation are required. To investigate and optimize this sequence, it was first applied to dipeptide **11** (Scheme 4).

In principle, the benzoyl substituent can be directly introduced by acylation of the glycine ester enolate using activated benzoic acid derivatives,[32] but in this case, the

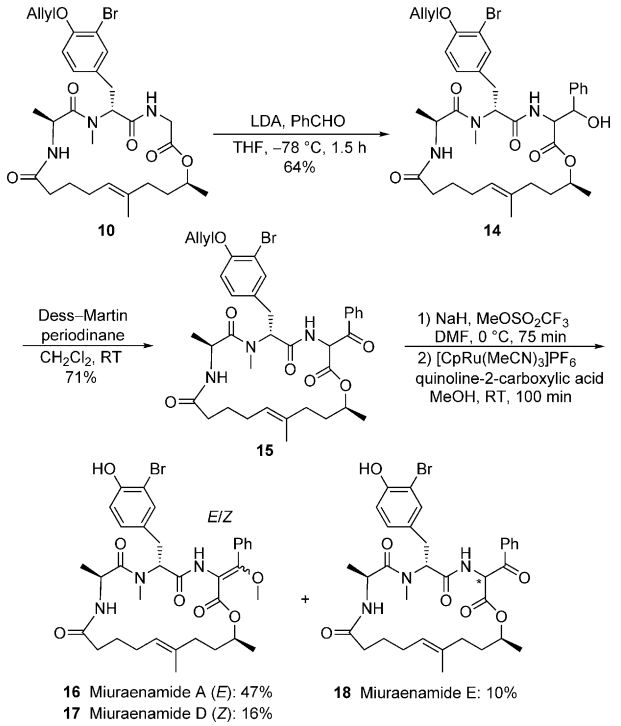


Scheme 4. Synthesis of the unusual miuraenamide side chain. LDA = lithium diisopropylamide.

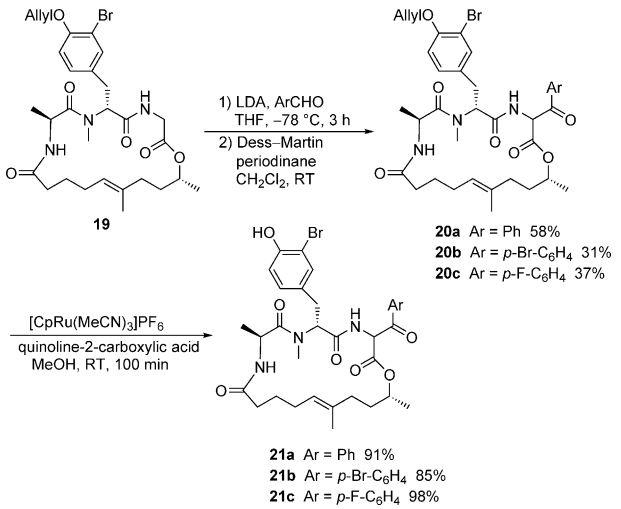
yields were only moderate (≤40%). Better results were obtained with a two-step procedure, combining an aldol addition with a subsequent Dess–Martin oxidation. The aldol reaction (with 3.5 equiv of LDA) provided a mixture of several stereoisomers, which, however, is irrelevant for our synthesis, as these stereogenic centers are removed again during the oxidation step. Subsequent O-methylation of dipeptide **12** was not as easy as expected. Attempts to employ trimethyl orthoformate/TsOH failed as did the use of NaH/MeI. In this case, exclusive N-methylation and racemization of the tyrosine were observed. Finally, NaH and methyl triflate were found to be the reagents of choice. Only one isomer of enol ether **13** was obtained in 77% yield and found to have the required *E* configuration, as determined by NOESY NMR spectroscopy.

These optimized conditions were then applied to the modification of macrocycle **10** (Scheme 5). Deprotonation with LDA (5 equiv) resulted in the formation of a deep red, slightly jelly-like solution of the enolate, which was then subjected to an aldol reaction using benzaldehyde, giving rise to modified cycle **14**. Owing to the excess of base, the product of the base-catalyzed isomerization of the O allyl protecting group to the corresponding *Z*-configured vinyl ether was formed in 2%,[33] but this had no significant influence on the further synthesis. Subsequent DMP oxidation gave rise to ketone **15**, which was subjected to O-methylation. However, for this more complex substrate, the reaction under the previously optimized conditions did not proceed to completion and delivered a mixture of the *E*- and *Z*-configured enol ethers, together with unreacted ketone **15**. As all three compounds are precursors of natural products, the mixture was directly subjected to O deallylation using $[CpRu(MeCN)_3]PF_6$ as the catalyst and quinolinecarboxylic acid as the ligand in methanol;[34] this process provided miuraenamide A (47%), miuraenamide D (16%), and miuraenamide E (10%), which could easily be separated by flash column chromatography. Unlike miuraenamide A, which could be obtained in pure form, miuraenamide D was always contaminated with some mol% of miuraenamide E. Obviously, the *Z* isomer is more sensitive towards hydrolysis than the *E* isomer, and miuraenamide E might thus be an artifact of the natural product isolation and purification process.

To determine whether the configuration of the secondary ester is relevant for the biological activity and to illustrate the flexibility of our synthetic route, cyclopeptide **19** (the



Scheme 5. Synthesis of miuraenamides A, D, and E.



Scheme 6. Synthesis of miuraenamide E analogues.

diastereomer of **10**) was also subjected to several aldol reactions (Scheme 6). The aldol products were directly subjected to Dess–Martin oxidation to obtain the corresponding ketones. Whereas in case of **15**, one diastereomer was formed almost exclusively (97:3 d.r.), ketones **20** were obtained as a 3:1 diastereomeric mixture. Cleavage of the allyl ether gave rise to the miuraenamide E analogues **21** in consistently high yields.

The biological activities of miuraenamides **16**–**18** and **21** as well as their synthetic precursors towards several tumor cell lines were then investigated (Table 1). The precursors of the

Table 1: IC_{50} values [nM] of miuraenamide derivatives towards different human tumor cell lines.[a]

Compund	HCT-116	HepG2	HL-60	U-2 OS
10	1128	n.d.	n.d.	n.d.
14	163	n.d.	n.d.	849
15	345	n.d.	n.d.	971
16	5.8	13.7	8.2	9.2
17	3.7	17.8	6.4	23.1
18	14.0	79.6	18.6	51.1
19	33300	n.d.	n.d.	33800
20a	8000	n.d.	n.d.	11700
20b	6900	n.d.	n.d.	8800
20c	4500	n.d.	n.d.	5600
21a	61.1	n.d.	n.d.	186
21b	30.7	n.d.	n.d.	136
21c	123	n.d.	n.d.	160

[a] HCT-116: colon carcinoma; HepG2: hepatocellular carcinoma; HL-60: acute promyelocytic leucemia; U-2 OS: bone osteosarcoma. n.d. = not determined.

miuraenamides that bear the allyl protecting group on the tyrosine unit already showed a significant cytotoxicity in the high nanomolar or low micromolar range towards colon cancer and osteosarcoma cell lines. The deprotected natural products themselves gave IC_{50} values in the low nanomolar range towards several tumor cell lines and were approximately two orders of magnitude more active than their precursors. The activities of isomers **16** (*E*) and **17** (*Z*) were comparable and slightly better than that of hydrolysis product **18**. Inversion of the stereogenic center resulted in a significant drop in activity (by a factor of 10–30) for the allyl-protected precursors (**20**), whereas the halogenated derivatives **20b** and **20c** were found to be slightly more active. The halogenated miuraenamide analogues **21b** and **21c**, with an inverted stereocenter in the polyketide chain, still gave IC_{50} values in the nanomolar range, but their activities were lower than that of miuraenamide E (by a factor of 2–9).

Miuraenamide A was already identified as a hit compound during a high-content screening campaign as it showed a strong influence on the morphology of the cytoplasm and nucleus of HeLa cells.[14] This effect was explained by a stabilization of the actin filaments and could be confirmed with our synthetic miuraenamide A sample (**16**; Figure 2). Treatment of cancer cells with **16** in low nanomolar amounts (2–20 nM) resulted in the formation of condensation spots of actin in the region of the nuclei. At higher concentrations (50–100 nM), nuclear condensation was observed, and the actin skeleton collapsed completely.

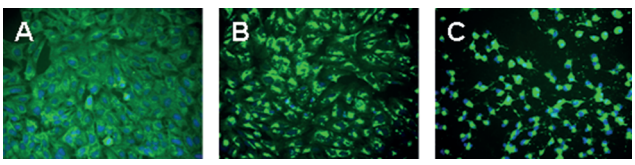


Figure 2. a—c) U-2 OS cells were treated with MeOH (0.5 vol%, a), **16** (20 nM, b), and **16** (100 nM, c) for 14 hours, and the actin filaments were visualized by immunofluorescence.

Comparable effects were observed with other cyclodepsipeptides, such as jasplakinolide[35] and chondramide,[10,36] which are also active in the low nanomolar range. Owing to the modular nature of the miuraenamide total synthesis, specific variations of individual buildings blocks should be feasible and provide information on structure–activity relationships, which should in turn enable the identification of derivatives with improved activities. Ongoing biological studies focus on the characterization of the binding to actin and the influence of this event on apoptotic processes in tumor cells.

In conclusion, we have shown that the miuraenamides can be easily obtained by a peptide modification approach. The miuraenamides are the structurally simplest representatives of a group of cyclodepsipeptides that all address the actin skeleton of a cell. The miuraenamides show high cytotoxicity towards a range of tumor cell lines with IC_{50} values in the low nanomolar range. The concept of introducing the unusual side chain in the final stage of the synthesis should allow the synthesis of libraries of miuraenamide derivatives for structure–activity relationship studies. Further investigations are currently in progress.

Keywords: actin-binding compounds · antitumor activity · cyclodepsipeptides · miuraenamides · natural products

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[1] a) P. Wipf, *Chem. Rev.* **1995**, *95*, 2115–2134; b) Y. Hamada, T. Shioiri, *Chem. Rev.* **2005**, *105*, 4441–4482; c) F. von Nussbaum, M. Brands, B. Hinzen, S. Weigand, D. Häbich, *Angew. Chem. Int. Ed.* **2006**, *45*, 5072–5129; *Angew. Chem.* **2006**, *118*, 5194–5254; d) F. Desriac, C. Jégou, E. Balnois, B. Brillet, P. Le Chevalier, Y. Fleury, *Mar. Drugs* **2013**, *11*, 3632–3660.

[2] a) P. Crews, L. V. Manes, M. Boehler, *Tetrahedron Lett.* **1986**, *27*, 2797–2800; b) J. C. Braekman, D. Daloze, B. Moussiaux, R. Riccio, *J. Nat. Prod.* **1987**, *50*, 994–995.

[3] a) W. R. Chan, W. F. Tinto, P. S. Manchand, L. J. Todaro, *J. Org. Chem.* **1987**, *52*, 3091–3093; b) E. D. De Silva, R. J. Andersen, T. M. Allen, *Tetrahedron Lett.* **1990**, *31*, 489–492.

[4] For studies on jasplakinolide, see: a) U. Schmidt, W. Siegel, K. Mundinger, *Tetrahedron Lett.* **1988**, *29*, 1269–1270; b) S. Kato, Y. Hamada, T. Shioiri, *Tetrahedron Lett.* **1988**, *29*, 6465–6466; for studies on geodiamolide, see: c) P. A. Grieco, A. Perez-Medrano, *Tetrahedron Lett.* **1988**, *29*, 4225–4228; d) J. D. White, J. C. Amedio, Jr., *J. Org. Chem.* **1989**, *54*, 736–738.

[5] Y. Y. Xu, C. Liu, Z. P. Liu, *Curr. Org. Synth.* **2013**, *10*, 67–89.

[6] a) S. C. Posey, B. E. Bierer, *J. Biol. Chem.* **1999**, *274*, 4259–4265; b) X. Zhang, X. Cui, L. Cheng, X. Guan, H. Li, X. Li, M. Chung, *Plos One* **2012**, *7*, e50899; c) L. Xie, A. Forer, *Cell Motil. Cytoskeleton* **2008**, *65*, 876–889.

[7] a) C. Odaka, M. L. Sanders, P. Crews, *Clin. Diagn. Lab. Immunol.* **2000**, *7*, 947–952; b) D. P. Cioca, K. Kitano, *Cell. Mol. Life Sci.* **2002**, *59*, 1377–1387.

[8] V. M. Freitas, M. Rangel, L. F. Bisson, R. G. Jaeger, G. M. Machado-Santelli, *J. Cell. Physiol.* **2008**, *216*, 583–594.

[9] a) B. Kunze, R. Jansen, F. Sasse, G. Höfle, H. Reichenbach, *J. Antibiot.* **1995**, *48*, 1262–1266; b) R. Jansen, B. Kunze, H. Reichenbach, G. Höfle, *Liebigs Ann.* **1996**, 285–290.

[10] a) U. Eggert, R. Diestel, F. Sasse, R. Jansen, B. Kunze, M. Kalesse, *Angew. Chem. Int. Ed.* **2008**, *47*, 6478–6482; *Angew. Chem.* **2008**, *120*, 6578–6582; b) H. Waldmann, T. S. Hu, S. Renner, S. Menninger, R. Tannert, T. Oda, H. D. Arndt, *Angew. Chem. Int. Ed.* **2008**, *47*, 6473–6477; *Angew. Chem.* **2008**, *120*, 6573–6577; c) A. Schmauder, L. D. Sibley, M. E. Maier, *Chem. Eur. J.* **2010**, *16*, 4328–4336; d) A. Zhdanko, A. Schmauder, C. I. Ma, L. D. Sibley, D. Sept, F. Sasse, M. E. Maier, *Chem. Eur. J.* **2011**, *17*, 13349–13357.

[11] F. Sasse, B. Kunze, T. M. A. Gronewold, H. Reichenbach, *J. Natl. Cancer Inst.* **1998**, *90*, 1559–1563.

[12] a) T. Iizuka, Y. Jojima, R. Fudou, S. Yamanaka, *FEMS Microbiol. Lett.* **1998**, *169*, 317–322; b) T. Iizuka, Y. Jojima, R. Fudou, A. Hiraishi, J. W. Ahn, S. Yamanaka, *Int. J. Syst. Evol. Microbiol.* **2003**, *53*, 189–195; c) Y. Q. Zhang, Y. Z. Li, B. Wang, Z.-H. Wu, C.-Y. Zhang, X. Gong, Z.-J. Qiu, Y. Zhang, *Appl. Environ. Microbiol.* **2005**, *71*, 3331–3336.

[13] a) T. Iizuka, R. Fudou, Y. Jojima, S. Ogawa, S. Yamanaka, Y. Inukai, M. Ojika, *J. Antibiot.* **2006**, *59*, 385–391; b) M. Ojika, Y, Inukai, Y. Kito, M. Hirata, T. Iizuka, R. Fudou, *Chem. Asian J.* **2008**, *3*, 126–133.

[14] E. Sumiya, H. Shimogawa, H. Sasaki, M. Tsutsumi, K. Yoshita, M. Ojika, K. Suenaga, M. Uesugi, *ACS Chem. Biol.* **2011**, *6*, 425–431.

[15] S. Rachid, D. Krug, B. Kunze, I. Kochems, M. Scharfe, T. M. Zabriskie, H. Blöcker, R. Müller, *Chem. Biol.* **2006**, *13*, 667–681.

[16] B. Böhlendorf, M. Herrmann, H. J. Hecht, F. Sasse, E. Forche, B. Kunze, H. Reichenbach, G. Höfle, *Eur. J. Org. Chem.* **1999**, 2601–2608.

[17] a) A. Ullrich, Y. Chai, D. Pistorius, Y. A. Elnakady, J. E. Herrmann, K. J. Weissman, U. Kazmaier, R. Müller, *Angew. Chem. Int. Ed.* **2009**, *48*, 4422–4425; *Angew. Chem.* **2009**, *121*, 4486–4489; b) A. Ullrich, J. Herrmann, R. Müller, U. Kazmaier, *Eur. J. Org. Chem.* **2009**, 6367–6378; c) Y. Chai, D. Pistorius, A. Ullrich, K. J. Weissman, U. Kazmaier, R. Müller, *Chem. Biol.* **2010**, *17*, 296–309; d) U. Kazmaier, A. Ullrich, J. Hoffmann, *Open Nat. Prod. J.* **2013**, *6*, 12–30.

[18] a) D. Seebach, *Aldrichimica Acta* **1992**, *25*, 59–66; b) D. Seebach, A. K. Beck, A. Studer in *Modern Synthetic Methods*, *Vol. 7* (Eds.: B. Ernst, C. Leumann), HCA/VCH, Basel, Weinheim, **1995**, pp. 1–178; c) D. Seebach, H. Bossler, H. Gründler, S. I. Shoda, R. Wenger, *Helv. Chim. Acta* **1991**, *74*, 197–224.

[19] D. Seebach, A. K. Beck, H. G. Bossler, C. Gerber, S. Y. Ko, C. W. Murtiashaw, R. Naef, S.-I. Shoda, A. Thaler, M. Krieger, R. Wenger, *Helv. Chim. Acta* **1993**, *76*, 1564–1590.

[20] a) U. Kazmaier, *J. Org. Chem.* **1994**, *59*, 6667–6670; b) U. Kazmaier, S. Maier, *J. Chem. Soc. Chem. Commun.* **1998**, 2535–2536; c) U. Kazmaier, S. Maier, *J. Org. Chem.* **1999**, *64*, 4574–4575; d) U. Kazmaier, S. Maier, *Org. Lett.* **1999**, *1*, 1763–1766; e) S. Maier, U. Kazmaier, *Eur. J. Org. Chem.* **2000**, 1241–1251.

[21] a) U. Kazmaier, S. Maier, F. L. Zumpe, *Synlett* **2000**, 1523–1535; b) J. Deska, U. Kazmaier, *Curr. Org. Chem.* **2008**, *12*, 355–385; c) U. Kazmaier, A. Bayer, J. Deska, *Synthesis* **2013**, 1462–1468.

[22] J. Deska, U. Kazmaier, *Angew. Chem. Int. Ed.* **2007**, *46*, 4570–4573; *Angew. Chem.* **2007**, *119*, 4654–4657.

[23] a) U. Kazmaier, J. Deska, A. Watzke, *Angew. Chem. Int. Ed.* **2006**, *45*, 4855–4858; *Angew. Chem.* **2006**, *118*, 4973–4976; b) J. Deska, U. Kazmaier, *Chem. Eur. J.* **2007**, *13*, 6204–6211; c) K. Krämer, J. Deska, C. Hebach, U. Kazmaier, *Org. Biomol. Chem.* **2009**, *7*, 103–110; d) J. Gorges, A. Ullrich, U. Kazmaier, *Eur. J. Org. Chem.* **2013**, 4372–4378.

[24] a) S. Datta, U. Kazmaier, *Org. Biomol. Chem.* **2011**, *9*, 872–880; b) S. Datta, A. Bayer, U. Kazmaier, *Org. Biomol. Chem.* **2012**, *10*, 8268–8275.

[25] W. S. Johnson, L. Werthemann, W. R. Bartlett, T. J. Brocksom, T.-T. Li, D. J. Faulkner, M. R. Petersen, *J. Am. Chem. Soc.* **1970**, *92*, 741–743.

[26] J. A. Marshall, B. G. Sheaer, S. L. Crooks, *J. Org. Chem.* **1987**, *52*, 1236–1245.

[27] T. Inoue, T. Inaba, I. Umezawa, M. Yuasa, H. Itokawa, K. Ogura, K. Komatsu, H. Hara, O. Hoshino, *Chem. Pharm. Bull.* **1995**, *43*, 1325 – 1335.
[28] J. Coste, D. Le-Nguyen, B. Castro, *Tetrahedron Lett.* **1990**, *31*, 205 – 208.
[29] B. Neises, W. Steglich, *Angew. Chem. Int. Ed. Engl.* **1978**, *17*, 522 – 524; *Angew. Chem.* **1978**, *90*, 556 – 557.
[30] K. Bowden, I. M. Heilbron, E. R. H. Jones, B. C. L. Weedon, *J. Chem. Soc.* **1946**, 39 – 45.
[31] a) U. Schmidt, H. Griesser, A. Lieberknecht, J. Talbiersky, *Angew. Chem. Int. Ed. Engl.* **1981**, *20*, 280 – 281; *Angew. Chem.* **1981**, *93*, 271 – 272; b) U. Schmidt, H. Griesser, G. Haas, M. Kroner, B. Riedl, A. Schumacher, F. Sutoris, A. Haupt, F. Emling, *J. Peptide Res.* **1999**, *54*, 146 – 161.
[32] K. Schultz, L. Stief, U. Kazmaier, *Synthesis* **2012**, 600 – 604.
[33] C. Su, P. G. Williard, *Org. Lett.* **2010**, *12*, 5378 – 5381.
[34] S. Tanaka, H. Saburi, Y. Ishibashi, M. Kitamura, *Org. Lett.* **2004**, *6*, 1873 – 1875.
[35] M. R. Bubb, I. Spector, B. B. Beyer, K. M. Fosen, *J. Biol. Chem.* **2000**, *275*, 5163 – 5170.
[36] J. Herrmann, S. Hüttel, R. Müller, *ChemBioChem* **2013**, *14*, 1573 – 1580.

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