Total Syntheses of New Proansamitocin Derivatives by Ring-Closing Metathesis

Axel Meyer, Andreas Kirschning*

Institut für Organische Chemie und Zentrum für Biomolekulare Wirkstoffchemie (BMWZ), Leibniz Universität Hannover, Schneiderberg 1b, 30167 Hannover, Germany
E-mail: andreas.kirschning@uni-hannover.de

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Abstract: The enantioselective synthesis of two new proansamitocin derivatives is described. Macrocyclization is achieved by ring-closing metathesis of appropriate alkene and diene precursors.

Key words: ansamitocins, natural product synthesis, macrolactam antibiotics, ring-closing metathesis

Maytansine (**1**) was first isolated from the Ethiopian plant *Maytenus serrata*[1,2] and inhibits growth of different leucemia cell lines as well as human solid tumors at very low concentrations (10^{-3} to 10^{-7} g/mL). The ansamitocins P-1, P-2, P-3 **2** and P-4 **3**,[3–5], which are of microbial origin (*Actinosynnema pretiosum*), are closely related. All these maytansinoids consist of a 19-membered macrolactam ring and only differ in the side chain at C-3.

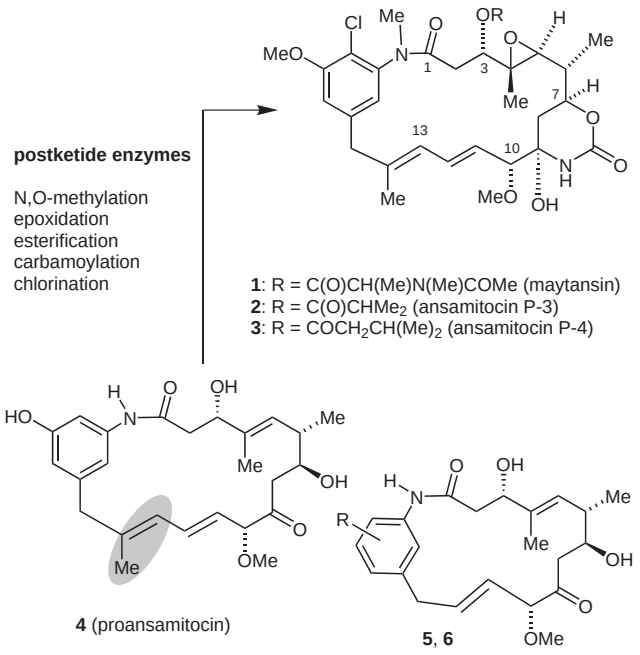

Figure 1 Structures of maytansinoids maytansin (**1**), ansamitocins P3 (**2**) and P4 (**3**) as well as proansamitocin (**4**) and 'mini'-proansamitocins **5** and **6**; biosynthetic relationship between ansamitocin P3 and proansamitocin

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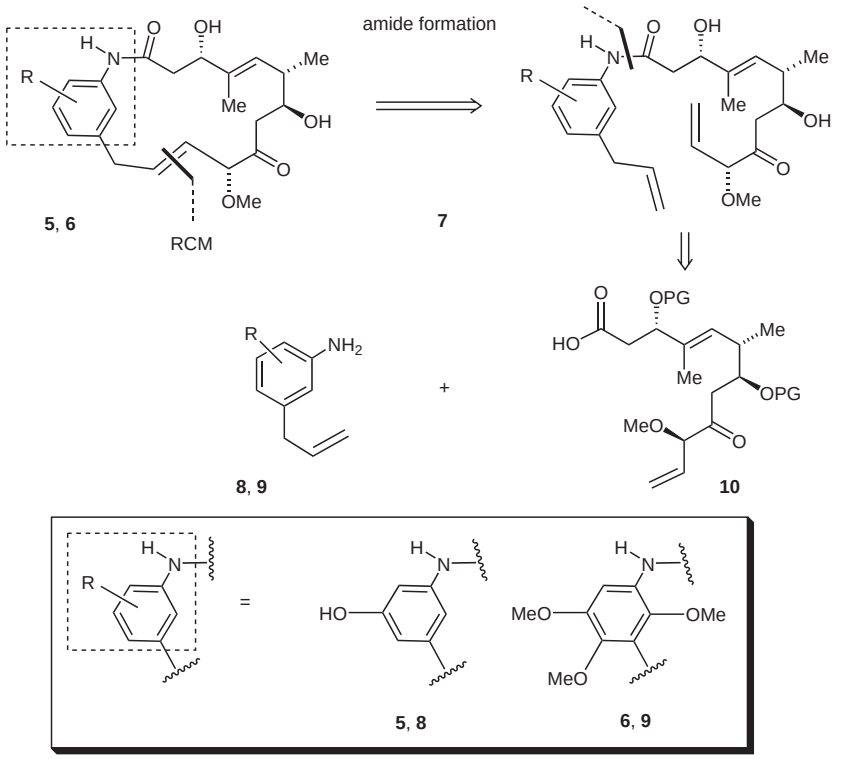
Despite their pharmaceutical potency, the clinical development of maytansinoids had to be stopped in phase II[2a,6] due to gastrointestinal side effects and neurotoxicities.[4b,7] However, efforts to develop them into clinically useful agents is still a major issue in pharmaceutical research. So far, knowledge of the structure–activity relationships[2a,e] has not relied on total synthesis but rather on semisynthetic approaches.[5,8] Therefore, minimum structural requirements for biological activity are still obscure. Mutasynthesis[9] and particularly conjugation of the ansamitocins to tumor-targeted antibodies for increasing pharmaceutical selectivity are currently the most promising strategies pursued in this field.[10]

Recently, we initiated a research program[11,12] dedicated to access new ansamitocins by synthetically exploiting the 3-amino-5-hydroxybenzoic acid (AHBA) block mutant of the ansamitocin P-3 producer *Actinosynnema pretiosum* (HGF073).[13] As part of this project we had to prepare proansamitocin (**4**), the polyketide ring-closure product, and analogues **5** and **6** which are basically 17-membered macrocycles missing the first propionate unit of the ketide chain (marked in **4** in Figure 1). Mutasynthesis of these advanced synthetic macrocycles would allow utilizing the postketide enzymes of *Actinosynnema pretiosum* (HGF073) for further functionalization (epoxidation, N,O-methylation, side-chain esterification, carbamoylation and chlorination). In this report we disclose a total synthesis approach toward two of these 'mini' proansamitocins **5** and **6**.

Our retrosynthetic analysis is summarized in Scheme 1. Key issues of the planned syntheses are a ring-closing metathesis (RCM) of **7** after intermolecular amide formation of anilines **8** and **9**, respectively, with ketide fragment **10**. We chose RCM for ring closure and not macrolactamization because in our hands the latter reaction often had turned out to be very problematic (low yields, double bond migration toward the keto group).[14]

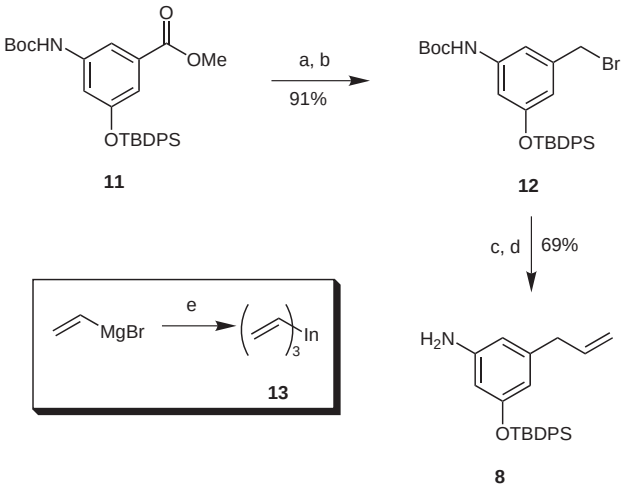
The syntheses of the two allylated anilines **8** and **9** are depicted in Schemes 2 and 3, respectively. Protected AHBA derivative **11**[15] was first transformed into benzyl bromide **12** which was treated with vinyl indium **13**[16] under Pd(0)-catalysis to yield aniline **8** after removal of the Boc-protection.

Trimethoxybenzene **14** was transformed into arylaldehyde **15** using standard electrophilic substitutions (Scheme 3). From there, benzyl bromide **16**,[17] which was

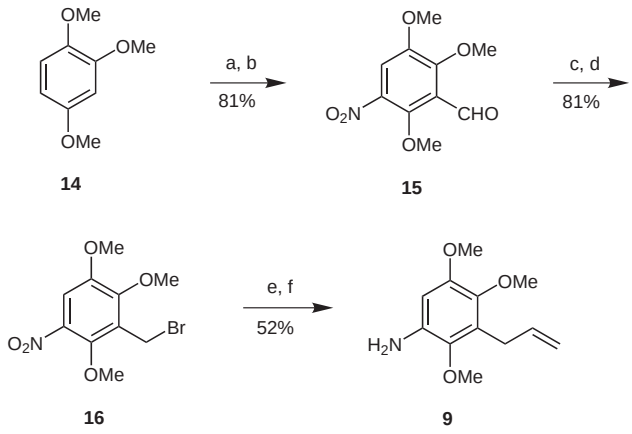


Scheme 1 Retrosynthetic analysis

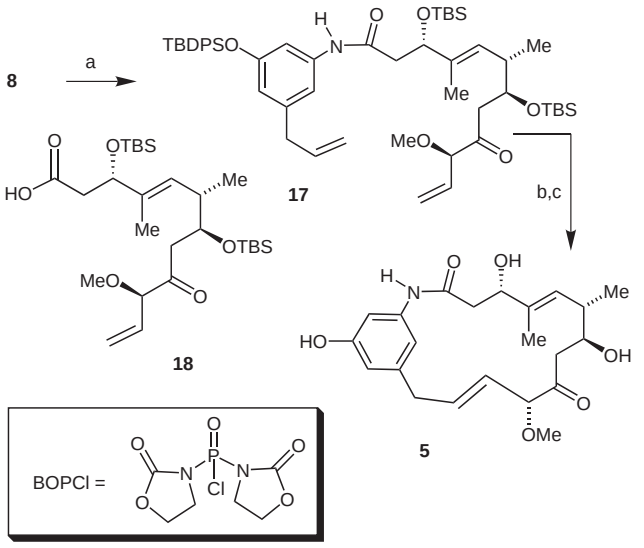
obtained after a reduction–bromination sequence, was subjected to the vinylation protocol described above. Finally, the amino group was liberated by reducing the nitro group. With both aromatic building blocks in hand, formation of the amide bond was envisaged for which we required the complex carboxylic acid **18**. The scalable synthesis of this ketide fragment was described before by us.[11] Among several amide-forming methods tested (Yamaguchi reagent, Mukaiyama conditions, DCC–DMAP) we found that BOPCl[18] acted as the best condensing agent yielding amide **17**[19] in satisfactory yield. Under the conditions given in Scheme 4 β-elimination of the TBSO group was suppressed to a minimum (<10%). Ring-closing metathesis (RCM)[20] using the 2nd generation Grubbs' catalyst afforded the macrocycle with pronounced preference for the *E*-isomer (*E*/*Z* >10:1) which was deprotected[21] to afford 'mini'-proansamitocin **5**.[22]



Scheme 2 *Reagents and conditions*: (a) DIBAL-H, CH_2Cl_2, –78 °C to r.t., 3.5 h (98%); (b) CBr_4, PPh_3, CH_2Cl_2, r.t., 30 min (93%); (c) **13**, Pd(dppf)Cl_2 (dppf: diphenylphosphinoferrocene), THF, Δ, 6 h (73%); (d) TFA, CH_2Cl_2, r.t., 2 h (95%); (e) $InCl_3$, THF, –78 °C, 0.5 h, then r.t. (73%).



Scheme 3 *Reagents and conditions*: (a) Et_2O, *n*-BuLi, DMF, 2 h, Δ (89%); (b) HOAc, concd HNO_3, 60 °C, 0.5 h (91%); (c) $NaBH_4$, THF, r.t., 1 h (99%); (d) PBr_3, pyridine, Et_2O, r.t., 0.5 h (82%); (e) **13**, formation in THF, –78 °C, 0.5 h, then r.t. and addition of Pd(dppf)Cl_2, 6 h, Δ, (68%); (f) $SnCl_2 \cdot 2H_2O$, EtOAc, Δ, 2.5 h (76%).

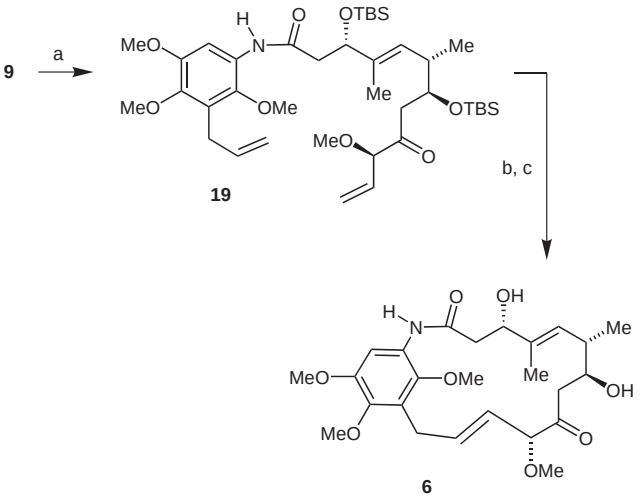


Scheme 4 *Reagents and conditions*: (a) BOPCl, **18**, DIPEA, CH_2Cl_2, 3 h, then addition of aniline **8**, DIPEA, CH_2Cl_2, 18 h (78%); (b) Grubbs' 2nd generation cat., CH_2Cl_2, D, 6 h (75%); (c) HF·py, THF, 16 h (94%).

In the same way and with similar efficiency we prepared proansamitocin **6**[22,23] via amide **19**[20](Scheme 5).

Preliminary biological tests (L929 fibroplasts from mice) revealed no significant cytotoxic activity of macrocycles **5** and **6** (in comparison: IC_{50} = 0.3 ng/mL for **2**) which points to the importance of the diene, the ester side chain and the carbamoyl group for the bioactive conformation of ansamitocines.

In conclusion, we prepared two new 17-membered macrocyclic derivatives of the maytansinoid proansamitocin. Both target compounds differed from the natural maytansinoids in the ring size and in part in the substitution pattern of the aromatic moiety. The total synthesis approach utilizes the scalable key fragment **18** and includes intermolecular amide formation using BOPCl as condensing agent and RCM as powerful and stereoselective macrocyclization method. The synthetic sequence presented can in principal be expanded to many new ansamitocin derivatives and thus will help to establish the minimum structural requirement for installing biological activity. Work is in progress to access more maytansinoids by conducting feeding experiments with *Actinosynnema pretiosum*[24] and to further reveal structure-activity relationships for these important antitumor agents.



Scheme 5 *Reagents and conditions*: (a) BOPCl, **18**, DIPEA, CH_2Cl_2, 3 h, then addition of aniline **9**, DIPEA, CH_2Cl_2, 18 h (63%); (b) Grubbs' 2nd generation cat., CH_2Cl_2, D, 6 h (75%); (c) HF·py, THF, 16 h (94%).

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References and Notes

(1) (a) Kupchan, S. M.; Komoda, Y.; Court, W. A.; Thomas, G. J.; Smith, R. M.; Karim, A.; Gilmore, C. J.; Haltiwanger, R. C.; Bryan, R. F. *J. Am. Chem. Soc.* **1972**, *94*, 1354. (b) Kupchan, S. M.; Komoda, Y.; Branfman, A. R.; Sneden, A. T.; Court, W. A.; Thomas, G. J.; Hintz, H. P. J.; Smith, R. M.; Karim, A.; Howie, G. A.; Verma, A. K.; Nagao, Y.; Dailey, R. G. Jr.; Zimmerly, V. A.; Sumner, W. C. Jr. *J. Org. Chem.* **1977**, *42*, 2349. (c) Bryan, R. F.; Gilmore, C. J.; Haltiwanger, R. C. *J. Chem. Soc., Perkin Trans. 2* **1973**, 897.

(2) Also from two other plant families *(Colubrina texensis*, *Rhamnaceae* and *Trewia nudiflora*, *Euphorbiaceae*) maytansinoids were isolated: (a) Reider, P. J.; Roland, D. M. *Maytansinoids* In *The Alkaloids*, Vol. 23; Brossi, A., Ed.; Academic Press: New York, **1984**, 71–156. (b) Wani, M. C.; Taylor, H. L.; Wall, M. E. *J. Chem. Soc., Chem. Commun.* **1973**, 390. (c) Powell, R. G.; Weisleder, D.; Smith, C. R. Jr.; Kozlowski, J.; Rohwedder, W. K. *J. Am. Chem. Soc.* **1982**, *104*, 4929. (d) Powell, R. G.; Smith, C. R. Jr.; Plattner, R. D.; Jones, B. E. *J. Nat. Prod.* **1983**, *46*, 660. (e) Smith, C. R. Jr.; Powell, R. G. In *Chemistry and Pharmacology of Maytansinoid Alkaloids* in *Alkaloids*, Vol. 2; Pelletier, S. W., Ed.; John Wiley and Sons: New York, **1984**, 149–204.

(3) (a) Higashide, E.; Asai, M.; Ootsu, K.; Tanida, S.; Kozai, Y.; Hasegawa, T.; Kishi, T.; Sugino, Y.; Yoneda, M. *Nature (London)* **1977**, *270*, 721. (b) Asai, M.; Mizuta, E.; Izawa, M.; Haibara, K.; Kishi, T. *Tetrahedron* **1979**, *35*, 1079.

(4) A mutant of *A. pretiosum* spp. *auranticum* provided 15 additional ansamitocines: (a) Izawa, M.; Tanida, S.; Asai, M. *J. Antibiot.* **1981**, *34*, 496. (b) Komoda, Y.; Kishi, T. *Maytansinoids*, In *Anticancer Agents Based on Natural Product Models*; Douros, J.; Cassady, J. M., Eds.; Academic Press: New York, **1980**, 353–389.

(5) (a) Rinehart, K. L. Jr.; Shield, L. S. *Fortschr. Chem. Org. Naturst.* **1976**, *33*, 231. (b) Cassady, J. M.; Chan, K. K.; Floss, H. G.; Leistner, E. *Chem. Pharm. Bull.* **2004**, *52*, 1.

(6) (a) Thigpen, J. T.; Ehrlich, C. E.; Creasman, W. T.; Curry, S.; Blessing, J. A. *Am. J. Clin. Oncol. (CCT)* **1985**, *6*, 273. (b) Thigpen, J. T.; Ehrlich, C. E.; Conroy, J.; Blessing, J. A. *Am. J. Clin. Oncol. (CCT)* **1985**, *6*, 427. (c) Ravry, M. J.; Omura, G. A.; Birch, R. *Am J. Clin. Oncol. (CCT)* **1985**, *8*, 148.

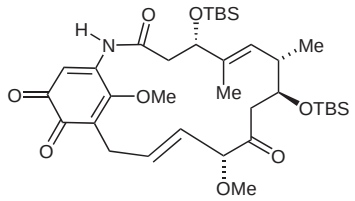
(7) Issell, B. F.; Crooke, S. T. *Cancer Treat. Rev.* **1978**, *5*, 199.
(8) (a) Chari, R. V.; Martell, B. A.; Gross, J. L.; Cook, S. B.; Shah, S. A.; Blättler, W. A.; McKenzie, S. J.; Goldmacher, V. S. *Cancer Res.* **1992**, *52*, 127. (b) Okamoto, K.; Harada, K.; Ikeyama, S.; Iwasa, S. *Jpn. J. Cancer Res.* **1992**, *83*, 761. (c) Liu, C.; Tadayoni, B. M.; Bourret, L. A.; Mattocks, K. M.; Derr, S. M.; Widdison, W. C.; Kedersha, N. L.; Ariniello, P. D.; Goldmacher, V. S.; Lambert, J. M.; Blättler, W. A.; Chari, R. V. J. *Proc. Nat. Acad. Sci. U.S.A.* **1996**, *93*, 8618.
(9) (a) These information were basically collected from semisynthetic work starting with the natural products as recently described by: Widdsion, W. C.; Wilhelm, S. D.; Cavanagh, E. E.; Whiteman, K. R.; Leece, B. A.; Kovtun, Y.; Goldmacher, V. S.; Xie, H.; Steeves, R. M.; Lutz, R. J.; Zhao, R.; Wang, L.; Blättler, W. A.; Chari, R. V. J. *J. Med. Chem.* **2006**, *49*, 4392; and in references 2a and 2e.
(b) Recent review of total synthesis approaches is given in ref. 5b.
(10) Weist, S.; Süssmuth, R. D. *Appl. Microbiol. Biotechnol.* **2005**, *68*, 141.
(11) Frenzel, T.; Brünjes, M.; Quitschalle, M.; Kirschning, A. *Org. Lett.* **2006**, *8*, 135.
(12) Kubota, T.; Brünjes, M.; Frenzel, T.; Xu, J.; Kirschning, A.; Floss, H. G. *ChemBioChem* **2006**, *7*, 1221.
(13) Yu, T.-W.; Bai, L.; Clade, D.; Hoffmann, D.; Toelzer, S.; Trinh, K. Q.; Xu, J.; Moss, S. J.; Leistner, E.; Floss, H. G. *Proc. Nat. Acad. Sci. U.S.A.* **2002**, *99*, 7968.
(14) Kashin, D.; Meyer, A.; Wittenberg, R.; Schöning, K.-U.; Gommlich, S.; Kirschning, A. *Synthesis* **2007**, 304.
(15) Becker, A. M.; Rickards, R. W.; Brown, R. F. C. *Tetrahedron* **1983**, *39*, 4189.
(16) Other vinylmetal species such as vinylstannane and vinylzinc only gave reduced yields of the coupling product in Pd(0)-catalyzed cross-coupling reactions: Pérez, I.; Pérez Sestelo, J.; Sarandeses, L. A. *J. Am. Chem. Soc.* **2001**, *123*, 4155.
(17) Andrus, M. B.; Meredith, E. L.; Soma Sekhar, B. B. V. *Org. Lett.* **2001**, *6*, 259.
(18) Cabré, J.; Palomo, A. L. *Synthesis* **1984**, 413.
(19) **General Procedure for the Preparation of Amides 17 and 19**: Ketoacid **18** (1 equiv) was dissolved in CH_2Cl_2, then treated with BOPCl (1 equiv) and DIPEA (1 equiv) and stirred at r.t. for 3 h. A solution of aniline **8**/**9** (1 equiv) and DIPEA (1 equiv) in CH_2Cl_2 was added over a period of 2 h. After completion (ca. 18 h), the reaction was terminated by addition of aq phosphate buffer (pH 7) and CH_2Cl_2. The organic phases were combined, dried over Na_2SO_4 and the solvent was removed under reduced pressure. Flash column chromatography over silica eluting with hexanes–EtOAc (20:1) furnished the corresponding amide **17**/**19**.
Spectroscopic data for **17**: $[\alpha]_D^{20}$ –59.0 (*c* = 1.2, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$; $CHCl_3$ = 7.26 ppm): δ = 7.69–7.71 (m, 4 H, OTBDPS), 7.50 (s, 1 H, NH), 7.33–7.43 (m, 6 H, OTBDPS), 6.95 (s, 1 H, ArH), 6.83 (s, 1 H, ArH), 6.27 (s, 1 H, ArH), 5.73 (ddt, *J* = 6.7, 10.2, 16.9 Hz, 1 H, 2′-H), 5.67 (ddd, *J* = 6.9, 10.3, 17.2 Hz, 1 H, 11-H), 5.44 (ddd, *J* = 1.3, 1.3, 17.2 Hz, 1 H, 12-H), 5.37 (ddd, *J* = 1.3, 1.3, 10.3 Hz, 1 H, 12-H′), 5.33–5.37 (m, 1 H, 5-H), 4.92 (ddd, *J* = 1.6, 1.6, 17.1 Hz, 1 H, 3′-H), 4.89 (ddd, *J* = 1.6, 1.6, 17.1 Hz, 1 H, 3′-H′), 4.39 (dd, *J* = 3.5, 7.3 Hz, 1 H, 3-H), 4.01–4.06 (m, 2 H, 7-H, 10-H), 3.33 (s, 3 H, 10-OCH_3), 3.13 (s, 1 H, 1′-H), 3.12 (s 1 H, 1′-H′), 2.66 (dd, *J* = 6.7, 17.2 Hz, 1 H, 8-H), 2.57 (dd, *J* = 4.6, 17.2 Hz, 1 H, 8-H′), 2.47–2.52 (m, 1 H, 6-H), 2.42 (dd, *J* = 3.8, 13.8 Hz, 1 H, 2-H), 2.36 (dd, *J* = 7.8, 13.8 Hz, 1 H, 2-H′), 1.59 (d, *J* = 1.6 Hz, 3 H, 4-CH_3), 1.08 (s, 9 H, OTBDPS), 0.86 (d, *J* = 7.0 Hz, 3 H, 6-CH_3), 0.84 [s, 9 H, $OSiC(CH_3)_3$], 0.82 [s, 9 H, $OSiC(CH_3)_3$], 0.05 (s, 3 H, $OSiCH_3$), –0.02 (s, 3 H, $OSiCH_3$), –0.03 (s, 3 H, $OSiCH_3$), –0.06 (s, 3 H, $OSiCH_3$). ^{13}C NMR (100 MHz, $CDCl_3$ = 77.0 ppm): δ = 206.8 (s, C-9), 169.1 (s, C-1), 155.9 (s, Ar), 141.7 (s, Ar), 138.7 (s, Ar), 136.8 (d, C-2′), 136.5 (s, C-4), 135.5 (d, Ph), 132.9 (s, Ph), 132.4 (d, C-11), 129.8 (d, Ph), 128.3 (d, C-5), 127.7 (d, Ph), 120.3 (t, C-12), 115.9 (d, Ar), 115.8 (t, C-3′), 112.7 (d, Ar), 108.9 (d, Ar), 88.8 (d, C-10), 75.2 (d, C-3), 71.4 (d, C-7), 57.0 (q, 10-OCH_3), 46.1 (t, C-2), 43.4 (t, C-8), 39.9 (t, C-1′), 38.2 (d, C-6), 26.5 [q, $OSi(Ph_2)C(CH_3)_3$], 26.0 {q, $OSi[(CH_3)_2]C(CH_3)_3$}, 25.8 {q, $OSi[(CH_3)_2]C(CH_3)_3$}, 19.5 [s, $OSi(Ph_2)C(CH_3)_3$], 18.1 {s, $OSi[(CH_3)_2]C(CH_3)_3$}, 18.0 {s, $OSi[(CH_3)_2]C(CH_3)_3$}, 16.2 (q, 6-CH_3), 12.5 (q, 4-CH_3), –4.5 [q, 2 × $OSiC(CH_3)_3$], –4.7 [q, $OSiC(CH_3)_3$], –5.2 [q, $OSiC(CH_3)_3$]. HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{52}H_{79}Si_3NO_6$: 898.5294; found: 898.5288. **19**: $[\alpha]_D^{20}$ –37.5 (*c* = 0.8, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$; $CHCl_3$ = 7.26 ppm): δ = 7.97 (s, 1 H, ArH), 7.77 (s, 1 H, NH), 5.99 (ddt, *J* = 6.1, 10.3, 16.7 Hz, 1 H, 2′-H), 5.68 (ddd, *J* = 6.9, 10.3, 17.2 Hz, 1 H, 11-H), 5.45 (ddd, *J* = 1.3, 1.3, 17.2 Hz, 1 H, 12-H), 5.40–5.43 (m, 1 H, 5-H), 5.38 (ddd, *J* = 1.3, 1.3, 10.3 Hz, 1 H, 12-H′), 5.00 (ddd, *J* = 1.6, 3.3, 10.3 Hz, 1 H, 3′-H), 4.89 (dd, *J* = 1.6, 3.3, 16.7 Hz, 1 H, 3′-H′), 4.51 (dd, *J* = 3.8, 8.2 Hz, 1 H, 3-H), 4.07 (dt, *J* = 5.0, 6.6 Hz, 1 H, 7-H), 4.05 (ddd, *J* = 1.3, 1.3, 6.9 Hz, 1 H, 10-H), 3.83 (s, 3 H, $ArOCH_3$), 3.78 (s, 3 H, $ArOCH_3$), 3.69 (s, 3 H, $ArOCH_3$), 3.42 (dd, *J* = 1.4, 6.0 Hz, 2 H, 1′-H, 1′-H′), 3.34 (s, 3 H, 10-OCH_3), 2.69 (dd, *J* = 6.6, 17.1 Hz, 1 H, 8-H), 2.60 (dd, *J* = 4.8, 17.1 Hz, 1 H, 8-H′), 2.50 (m, 1 H, 6-H), 2.51 (dd, *J* = 3.8, 13.7 Hz, 1 H, 2-H), 2.44 (dd, *J* = 8.2, 13.7 Hz, 1 H, 2-H′), 1.65 (d, *J* = 1.0 Hz, 3 H, 4-CH_3), 0.85 (d, *J* = 4.4 Hz, 3 H, 6-CH_3), 0.84 [s, 9 H, $OSiC(CH_3)_3$], 0.83 [s, 9 H, $OSiC(CH_3)_3$], 0.05 (s, 3 H, $OSiCH_3$), 0.02 (s, 3 H, $OSiCH_3$), 0.01 (s, 3 H, $OSiCH_3$), –0.03 (s, 3 H, $OSiCH_3$). ^{13}C NMR (100 MHz, $CDCl_3$ = 77.0 ppm): δ = 206.8 (s, C-9), 169.1 (s, C-1), 149.1 (s, Ar), 143.3 (s, Ar), 140.8 (s, Ar), 137.1 (s, C-2′), 136.4 (s, C-4), 132.4 (d, C-11), 128.4 (d, C-5), 127.4 (s, Ar), 126.4 (s, Ar), 120.3 (t, C-12), 115.0 (t, C-3′), 103.4 (d, Ar), 88.9 (d, C-10), 75.4 (d, C-3), 71.4 (d, C-7), 61.5 (q, $ArOCH_3$), 60.9 (q, $ArOCH_3$), 56.9 (q, 10-OCH_3), 55.9 (q, $ArOCH_3$), 46.5 (t, C-2), 43.4 (t, C-8), 38.1 (d, C-6), 28.7 (t, C-1′), 25.9 {q, $OSi[(CH_3)_2]C(CH_3)_3$}, 25.8 {q, $OSi[(CH_3)_2]C(CH_3)_3$}, 18.1 {s, $OSi[(CH_3)_2]C(CH_3)_3$}, 18.0 {s, $OSi[(CH_3)_2]C(CH_3)_3$}, 16.0 (q, 6-CH_3), 12.4 (q, 4-CH_3), –4.5 [q, 2 × $OSiC(CH_3)_3$], –4.6 [q, $OSiC(CH_3)_3$], –5.2 [q, $OSiC(CH_3)_3$]. HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{39}H_{67}Si_2NO_8$: 756.4303; found: 756.4306.
(20) (a) Gradillas, A.; Pérez-Castells, J. *Angew. Chem. Int. Ed.* **2006**, *45*, 6086; *Angew. Chem.* **2006**, *118*, 6232.
(b) Lemarchand, A.; Bach, T. *Synthesis* **2005**, 1977.
(c) McErlean, C. S. P.; Proisy, N.; Davis, C. J.; Boland, N. A.; Sharp, S. Y.; Boxall, K.; Slawin, A. M. Z.; Workman, P.; Moody, C. J. *Org. Biomol. Chem.* **2007**, *5*, 531.
(21) Tetra-*n*-butylammonium fluoride (TBAF) turned out to be too basic for inducing the elimination of the siloxy group at C-3.
(22) **General Procedure for the Preparation of Macrocycles 5 and 6**: Amide **17**/**19** (1 equiv) was dissolved in anhyd CH_2Cl_2, treated with Grubbs' 2nd generation catalyst (0.2 equiv) and heated to reflux. After completion (ca. 6 h), the reaction was terminated by the addition of aq phosphate buffer (pH 7). The organic phases were combined, dried over Na_2SO_4 and the solvent was removed under reduced pressure. Flash column chromatography over silica with hexanes–EtOAc (20:1) as eluent yielded the corresponding protected macrolactams which were dissolved in anhyd THF and treated with HF·Py (ca. 70% HF, excess) at r.t. After

completion (ca. 16 h), the reaction mixture was neutralized with a sat. $NaHCO_3$ solution. The aqueous phase was extracted with EtOAc, the organic phases were combined, dried over Na_2SO_4 and the solvent was removed under reduced pressure. Flash column chromatography over silica with CH_2Cl_2–MeOH (50:1) as eluent yielded the corresponding macrolactam **5**/**6**.

Spectroscopic data for **5**: $[\alpha]_D^{20}$ –134.6 (*c* = 1.0, MeOH). ^{1}H NMR (400 MHz, CD_3OD; CH_3OH = 3.31 ppm): δ = 7.90 (s, 1 H, NH), 7.10 (dd, *J* = 1.6, 1.6 Hz, 1 H, ArH), 6.51 (dd, *J* = 2.1, 2.1 Hz, 1 H, ArH), 6.39 (dd, *J* = 1.6, 2.1 Hz, 1 H, ArH), 6.06 (dddd, *J* = 0.9, 6.7, 8.0, 15.5 Hz, 1 H, 12-H), 5.41 (psd, *J* = 9.3 Hz, 1 H, 5-H), 5.26 (ddt, *J* = 1.1, 8.1, 15.5 Hz, 1 H, 11-H), 4.31–4.37 (m, 2 H, 3-H, 10-H), 3.96 (ddd, *J* = 3.6, 8.5, 8.5 Hz, 1 H, 7-H), 3.32–3.35 (m, 2 H, 13-H, 13-H′), 3.33 (s, 3 H, 10-OCH_3), 2.75 (dd, *J* = 3.6, 13.7 Hz, 1 H, 2-H), 2.62 (dd, *J* = 6.6, 13.7 Hz, 1 H, 2-H), 2.50–2.54 (m, 2 H, 8-H, 8-H′), 2.44–2.49 (m, 1 H, 6-H), 1.66 (d, *J* = 0.9 Hz, 3 H, 4-CH_3), 0.96 (d, *J* = 6.3 Hz, 3 H, 6-CH_3). ^{13}C NMR (100 MHz, CD_3OD = 49.0 ppm): δ = 209.2 (s, C-9), 171.5 (s, C-1), 158.9 (s, Ar), 142.5 (s, Ar), 140.4 (s, Ar), 138.7 (s, C-4), 137.9 (d, C-12), 127.0 (d, C-5), 126.7 (d, C-11), 113.1 (d, Ar), 112.9 (d, Ar), 105.7 (d, Ar), 89.9 (d, C-10), 74.3 (d, C-7), 73.0 (d, C-3), 57.0 (q, 10-OCH_3), 44.7 (t, C-8), 42.6 (t, C-2), 40.0 (d, C-6), 39.3 (t, C-13), 17.7 (q, 6-CH_3), 14.7 (q, 4-CH_3). HRMS (ESI): *m*/*z* [M – H^+] calcd for $C_{22}H_{29}NO_6$: 402.1917; found: 402.1923.

6: ^{1}H NMR (400 MHz, CD_3OD; CH_3OH = 3.31 ppm): δ = 8.01 (t, *J* = 1.51 Hz, 1 H, ArH), 5.92 (dddd, *J* = 0.6, 3.4, 7.9, 15.5 Hz, 1 H, 12-H), 5.58 (psd, *J* = 8.5 Hz, 1 H, 5-H), 5.26 (dd, *J* = 7.0, 15.5 Hz, 1 H, 11-H), 4.40 (m, 1 H, 3-H), 4.21 (d, *J* = 7.0 Hz, 1 H, 10-H), 3.93 (ddd, *J* = 1.6, 8.9, 10.5 Hz, 1 H, 7-H), 3.82 (s, 3 H, $ArOCH_3$), 3.70–3.81 (m, 1 H, 13-H), 3.75 (s, 3 H, $ArOCH_3$), 3.68 (s, 3 H, $ArOCH_3$), 3.33 (s, 3 H, 10-OCH_3), 3.13–3.26 (m, 1 H, 13-H′), 2.92 (dd, *J* = 4.5, 16.7 Hz, 1 H, 2-H), 2.77 (dd, *J* = 3.1, 16.7 Hz, 1 H, 2-H′), 2.54 (dd, *J* = 1.6, 16.9 Hz, 1 H, 8-H), 2.29 (dd, *J* = 10.5, 16.9, 10.5 Hz, 1 H, 8-H′), 2.31 (m, 1 H, 6-H), 1.62 (s, 3 H, 4-CH_3), 1.01 (d, *J* = 6.3 Hz, 3 H, 6-CH_3). ^{13}C NMR (100 MHz, CD_3OD = 49.0 ppm): δ = 208.2 (s, C-9), 171.8 (s, C-1), 150.5 (s, Ar), 143.9 (s, Ar), 142.7 (s, Ar), 136.8 (s, Ar), 134.3 (d, C-12), 129.5 (s, C-4), 127.4 (d, C-5), 127.3 (s, Ar), 125.0 (d, C-11), 104.5 (d, Ar), 88.7 (d, C-10), 72.9 (d, C-7), 70.7 (d, C-3), 61.7 (q, $ArOCH_3$), 61.4 (q, $ArOCH_3$), 57.3 (q, 10-CH_3), 56.4 (q, $ArOCH_3$), 44.9 (t, C-2), 42.6 (t, C-8), 39.4 (d, C-6), 27.9 (t, C-13), 18.1 (q, 6-CH_3), 14.4 (q, 4-CH_3). HRMS (ESI): *m*/*z* [M + Na^+] calcd for $C_{25}H_{35}NO_8$: 500.2260; found: 500.2260.

(23) We tested oxidation [$(NH_4)_2Ce(NO_3)$, MeCN] of the aromatic moiety present in the silyl-protected precursor of **6** but could only isolate the *ortho*-quinone **20** (Figure 2 in 71% yield instead of the *para*-quinone present in geldanamycin. See also: (a) Andrus, M. B.; Meredith, E. L.; Hicken, E. J.; Simmons, B. L.; Glancey, R. R.; Ma, W. *J. Org. Chem.* **2003**, *68*, 8162. (b) Lemarchand, A.; Bach, T. *Tetrahedron* **2004**, *60*, 9659.



20

Figure 2

(24) Meyer, A.; Brünjes, M.; Taft, F.; Frenzel, F.; Sasse, F.; Kirschning, A.; unpublished results.