Asymmetric Syntheses of Potent Antitumor Macrolides Cryptophycin B and Arenastatin A

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Efficient and highly stereoselective syntheses of cryptophycin B and arenastatin A, potent cytotoxic agents, are described. An ester-derived titanium enolate mediated *syn*-aldol reaction was employed to generate the stereocenters C-5 and C-6. The route is convergent and provides a convenient access to the synthesis of structural variants of cryptophycins as well as members of its family.

Introduction

In 1990, while screening the extracts of blue-green algae for antitumor activity, researchers at Merck & Co., Inc. found a strong antifungal agent in the lipophilic extract of the cyanobacteria *Nostoc* sp. (ATCC 53789).[1] It was highly active against filamentous fungi and yeast of *Cryptococcus* sp. with MIC_{50} and MIC_{90} values of both 31 μg/mL and consequently, was given the name cryptophycin (**1**, Figure 1). Later Moore et al. isolated and identified 25 compounds from *Nostoc* sp. GSV 224 of which the four major constituents, named cryptophycin A (**1**), B (**2**), C (**3**) and D (**4**), showed excellent activities against solid tumors implanted in mice.[2−4] Cryptophycins A and B exhibited IC_{50} values of 5 and 7 pg/mL against KB cells and 3 and 0.2 pg/mL against LoVo cells, respectively.[2] In addition, the compounds were equally effective against drug-sensitive and drug-resistant tumor cells.[2,3] In vivo structure-activity relationship studies on all isolated cryptophycins showed that the exclusion of the chlorine atom from the D-tyrosine moiety generally reduced the cytoxicity 10-fold, although the potencies of cryptophycin A and B were almost identical.[4] Also, removal of the *O*-methyl group or elimination of the epoxide oxygen atom both resulted in loss in potency (up to 1000-fold). Interestingly, if the epoxide is converted into a chloro- or bromohydrin no decrease in cytotoxicity was observed.[6] Replacement of the isobutyl group of the L-leucic acid moiety by an *n*-propyl, isopropyl or *sec*-butyl group was accompanied by a considerable reduction in cytoxicity (10- to 100-fold). The lack of a methyl group adjacent to the epoxide group lessened the cytoxicity substantially.

In 1994 another potent member of the cryptophycin family was isolated from the Okinawan marine sponge *Dysidea arenaria* and identified by Kitagawa et al.[7] Arenastatin A (**5**), named after its origin, showed an excellent cytotoxicity of 5 pg/mL against KB cell line (IC_{50}).[7] Unfortunately, its potency is limited by the fact that it is subject to degradation in blood, a vulnerability caused by the high susceptibility of the ester linkages to hydrolysis.[8−11] Synthesis of triamide and carba analogs resulted in better in vivo stability, but reduced potency.[8]

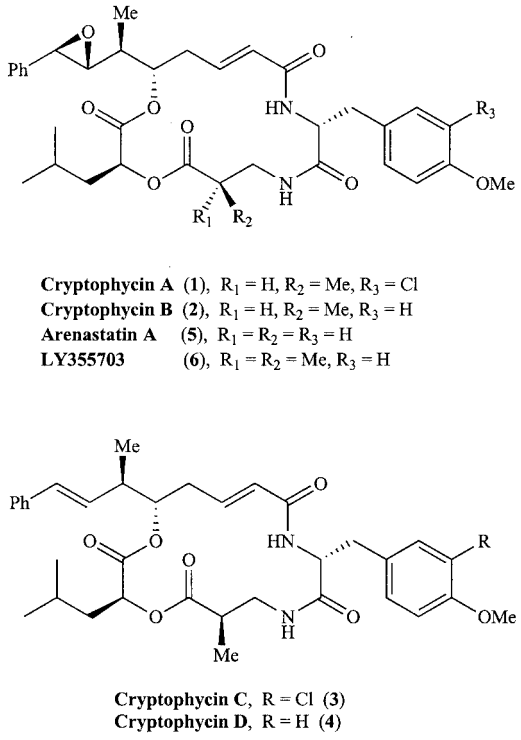

Figure 1. Structures of arenastatin A and cryptophycins

One of the more extensively investigated cryptophycins is cryptophycin A. It is an antimitotic and antiproliferative

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agent exhibiting antitumor activity against mammary, colon and pancreatic adenocarcinomas in mice through its interaction with microtubules. Cryptophycin A binds in vitro to tubulin within the vinca domain and inhibits tubulin polymerization, causes tubulin to aggregate and depolymerizes microtubules to linear polymers.[12,13] At low nanomolar concentrations, in the absence of microtubule depolymerization, cryptophycin A effectively stabilized microtubule dynamics by binding reversibly and with high affinity to the ends of microtubules.[2,14] Its actions cause mitotic arrest accompanied by the formation of abnormal mitotic spindles and condensed chromatin without effecting interphase microtubule structures. In addition, cryptophycins overcome a common form of multidrug resitance, P-glycoprotein-mediated efflux, since it is not a substrate for P-glycoprotein. In view of the potency of cryptophycins and the need for analogs that have a higher stability toward in vivo hydrolysis, many synthetic analogs of cryptophycins have been synthesized.[2−5,8−11,15−19] Cryptophycin 52 (**6**), also known as LY355703, and initially synthesized by Lilly Research Laboratories, is currently under clinical trial phase 2. LY355703 was selected due to its high hydrolytic stability and, nevertheless, very potent activity against tumor cell lines in culture.[20]

The significant clinical potential of the cryptophycins and their relatively low natural abundance has attracted immense interest in their synthesis and structural modification. Several total syntheses and synthetic approaches to cryptophycins and arenastatin A have been described in recent years.[21−40] As part of our interest in the structure-function studies of cryptophycins, we sought a flexible, enantioselective synthesis of cryptophycin B. Herein we report a convergent and stereocontrolled total synthesis of cryptophycin B and arenastatin A.

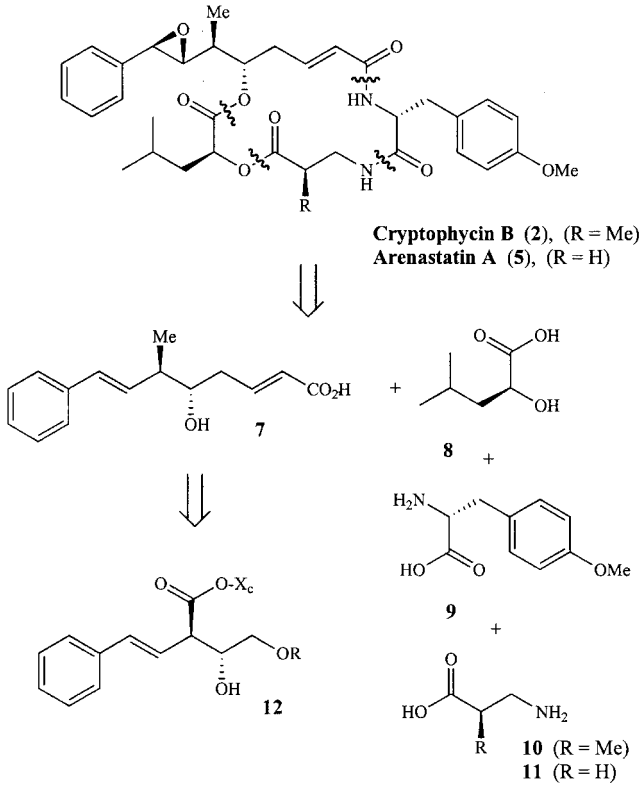
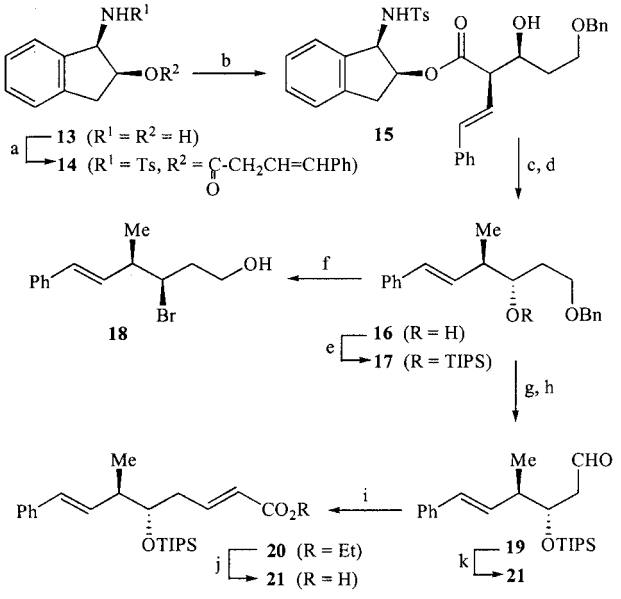


Figure 2. Retrosynthetic analysis

Results and Discussion

As outlined in Figure 2, we planned the assembly of cryptophycin B and arenastatin A in a convergent manner from octadienoic acid **7**, hydroxyisocaproic acid **8**, D-tyrosine derivative **9** and β-amino acid **10** or **11**, respectively. The fragments would be connected by Yamaguchi esterification and macrolactamization reactions. Introduction of the sensitive epoxide functionality would be carried out at the final stage of the synthesis. The stereocenters on C-5 and C-6 of fragment **7** would derive from *syn*-aldol adduct **12** generated by means of a titanium enolate mediated aldol reaction.

In order to set the two stereocenters on C-5 and C-6 of **7**, an ester-derived titanium enolate mediated *syn*-aldol reaction was employed.[41,42] The aldol starting material, ester **14** containing the chiral auxiliary and the styryl moiety, was derived by consecutive tosylation and acylation of (1*R*,2*S*)-1-aminoindan-2-ol (**13**) (Scheme 1). Thus, tosylation of the amine with TsCl and 2 equiv. of DMAP in DCM at 0 °C to room temperature for 1 h, followed by esterification with commercially available (*E*)-4-phenyl-3-butenoic acid and



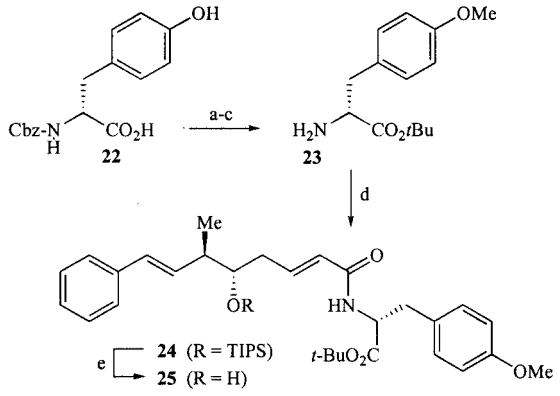
Scheme 1. (a) TsCl, DMAP, CH_2Cl_2, 0 °C, 1 h, then PhCH=CHCH$_2$CO$_2$H, EDCI, 23 °C, 6 h (98%); (b) $TiCl_4$, *i*Pr$_2$NEt, 0−23 °C, 1 h, then BnO(CH$_2$)$_2$CHO, −78 °C, 20 min (98%); (c) LAH, THF, 0 °C, 1 h (92%); (d) PhLi, THF, −78 °C, 30 min, then TsCl, −20 °C, 30 min, then LAH, 0 °C, 20 min (96%); (e) TIPSOTf, 2,6-lutidine, CH_2Cl_2, 23 °C, 20 min (99%); (f) BBr_3, 0 °C, 5 min (45%); (g) BBr_3, K_2CO_3, CH_2Cl_2, 0 °C, (83%); (h) PCC, MS (4 Å), CH_2Cl_2, 23 °C, 10 min (98%); (i) NaH, (EtO)$_2$P(O)CH$_2$CO$_2$Et, THF, 0 °C, 30 min (92%); (j) LiOH, EtOH/H$_2$O (1:1), 23 °C, 2 h (94%); (k) CH$_2$(CO$_2$H)$_2$, Et$_3$N, reflux, 4 h (33%)

EDCI at ambient temperature for 6 h furnished 98% of indanyl ester **14**. Exposure of ester **14** to $TiCl_4$ and iPr_2NEt in DCM at 0 °C to room temperature for 1 h to generate the (*Z*)-enolate and subsequent reaction with 3-(benzyloxy-)propionaldehyde at −78 °C for 20 min gave aldol product **15** in 98% yield and > 99% *de*.[41,42] When the enolate of **14** was treated with 3-[(*p*-methoxybenzyl)oxy]propionaldehyde the desired aldol product could not be obtained possibly due to the instability of the PMB group under the reaction conditions.

The auxiliary was cleaved by reduction of ester **15** with LAH in THF at 0 °C for 1 h. The resulting 1,3-diol was obtained in 92% yield and the auxiliary was also recovered in 92% yield. The primary alcohol was to be converted into the methyl group in a one-pot procedure by tosylation and subsequent reduction with hydride. Thus, treatment of the 1,3-diol with phenyllithium in THF at −78 °C for 30 min, subsequent addition of TsCl at −78 °C and warming of the reaction mixture to −20 °C furnished the primary tosylate in situ. Hydride reduction with LAH at −20 to 0 °C for 20 min gave alcohol **16** in 96% yield. The use of Super Hydride® resulted in comparable yields. The free alcohol was then protected as triisopropylsilyl ether **17** in quantitative yield by treatment of **16** with TIPSOTf and 2,6-lutidine in DCM at room temperature for 20 min.

In order to install the α,β-unsaturated carboxylic acid, the benzyl protecting group had to be removed selectively. Treatment of **17** with lithium or sodium in liquid ammonia partially reduced the styryl double bond and gave the desired primary alcohol only as minor product. The use of alternative benzyl ether cleaving reagents, such as TMSI, $FeCl_3$, $AlCl_3$, $BF_3{\cdot}Et_2O$ and DDQ, in a variety of solvents rendered no practical amount of desired product. Only treatment with BBr_3 in DCM at 0 °C cleanly removed the benzyl group, but unfortunately, converted the silyl ether into bromide **18** with inversion of configuration (only one isomer isolated). Silyloxy replacement might have been the consequence of the presence of HBr, therefore, in order to reduce the reactivity and acidity of BBr_3, treatment of **17** with BBr_3 was performed in DCM at 0 °C and in the presence of solid K_2CO_3. Rewardingly, the selectively unprotected alcohol was obtained in 83% yield. Oxidation to the corresponding aldehyde **19** was accomplished in 98% yield with PCC in DCM in the presence of molecular sieves (4 Å). A Horner−Emmons olefination of **19** with the sodium salt of triethyl phosphonoacetate in THF at 0 °C proceeded with 92% yield and rendered (*E*)-α,β-unsaturated ester **20** as the only isomer. Ester hydrolysis with LiOH in a 1:1 mixture of $EtOH/H_2O$ gave octadienoic acid **21** in 94% yield. The conversion of aldehyde **19** to acid **21** could also be achieved in one step by treatment with malonic acid and Et_3N in refluxing benzene, but in only 33% yield.

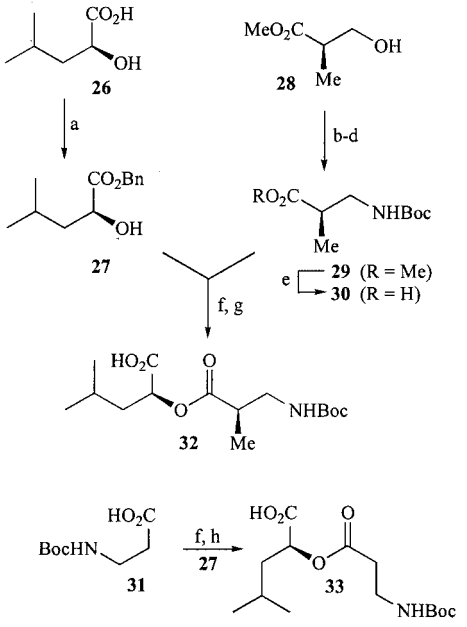
After generation of diene fragment **21**, the remaining macrolide sections had to be generated and successively connected. First, commercially available *N*-Cbz-D-tyrosine (**22**) was converted into the methyl phenyl ether in 91% by treatment with Me_2SO_4 and NaOH in refluxing EtOH



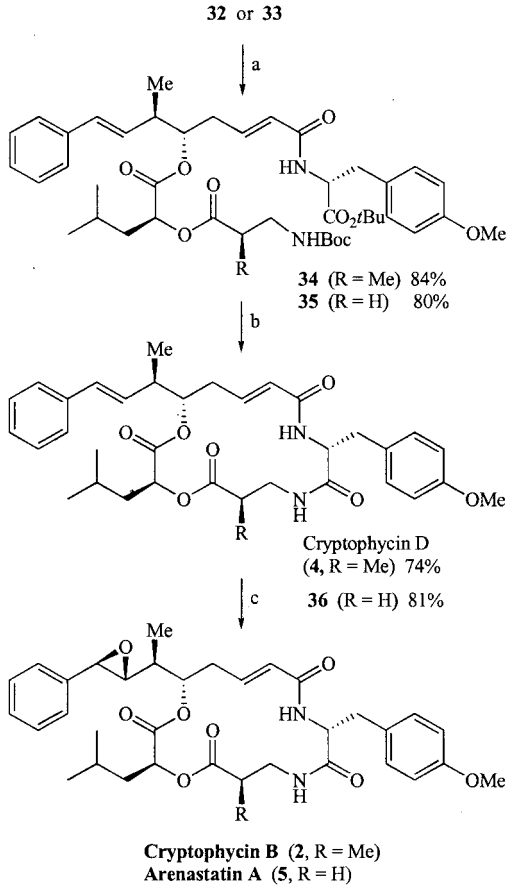
Scheme 2. (a) Me_2SO_4, NaOH, $EtOH/H_2O$ (50:1), reflux, 3 h (91%); (b) 2,4,6-$Cl_3C_6H_2COCl$, iPr_2NEt, THF, 23 °C, 30 min, then *t*BuOH, DMAP, toluene, 23 °C, 3 h (64%); (c) H_2, 5% Pd/C, MeOH, 2 h (95%); (d) **21**, EDCI, DMAP, 23 °C, 12 h (83%); (e) TBAF, THF, 23 °C, 6 h (99%)

(Scheme 2).[43] Esterification of the acid with *t*BuOH was achieved using Yamaguchi's conditions.[44] Thus, anhydride formation with trichlorobenzoyl chloride in the presence of Hünig's base and subsequent reaction with *t*BuOH and DMAP in toluene rendered fully protected D-tyrosine. Removal of the Cbz protection group was performed under hydrogen with 5% Pd/C catalyst in MeOH for 2 h and afforded tyrosine fragment **23** in 95% yield. The coupling of octadienoic acid fragment **21** with **23** was accomplished by exposure to EDCI and DMAP at ambient temperature for 12 h and gave α,β-unsaturated amide **24** in 83% yield. Removal of the silyl ether protecting group with TBAF in THF at room temperature gave alcohol **25** in 99% yield.

Next, L-leucic acid (**26**) was *O′*-benzylated by treatment with Cs_2CO_3 in $MeOH/H_2O$ (1:1) at ambient temperature for 30 min, followed by removal of the solvents and subsequent reaction with benzyl bromide in DMF at 0 °C to room temperature for 12 h (Scheme 3).[45] The synthesis of cryptophycin B required *N*-Boc-protected 3-amino-2-methylpropionic acid **30**, whereas *N*-Boc-protected β-alanine **31** was required for arenastatin A. Methylpropionic acid derivative **30** was derived from commercially available methyl (*R*)-2-methylpropionate (**28**) in a three-step sequence. The hydroxy group was tosylated by treatment with TsCl, Et_3N and DMAP in DCM at 0 °C in 91% yield. Quantitative conversion of the tosylate to *N*-Boc-protected amine **29** was attained in a one-pot procedure by reaction of the tosylate with NaN_3 in DMSO at room temperature and subsequent hydrogenation in the presence of 10% Pd/C and di-*tert*-butyl dicarbonate for 12 h. Saponification of ester **29** with LiOH in EtOH at room temperature for 30 min led to the free acid in quantitative yield. Acid **30** was then coupled with **27** using DCC and DMAP in DCM at room temperature for 12 h. The diester was obtained in 91% yield and debenzylated by hydrogenation in the presence of 5% Pd/C in EtOAc for 5 h to furnish desired fragment **32** in 95% yield. Fragment **33** for the synthesis of arenastatin A was obtained in two steps from known *N*-Boc-β-alanine[46] (**31**) (Scheme 3). Coupling of acid **31** with **27** was accomplished



Scheme 3. (a) Cs_2CO_3, MeOH/H_2O (5:1), 23 °C, 30 min, then BnBr, DMF, 0 °C, 12 h (quant.); (b) TsCl, Et_3N, CH_2H_2, 0 °C, 1 h (99%); (c) NaN_3, DMSO, 23 °C, 6 h; (d) Boc_2O, H_2, 10% Pd/C, EtOAc, 23 °C, 12 h (quant., 2 steps); (e) LiOH, EtOH, 23 °C, 30 min (quant.); (f) DCC, DMAP, CH_2Cl_2, 23 °C, 12 h (91%); (g) H_2, 5% Pd/C, EtOAc, 23 °C, 5 h (95%); (h) H_2, 10% Pd/C, EtOAc 23 °C, 1 h (97%)



Scheme 4. (a) 2,4,6-$Cl_3C_6H_2COCl$, *i*Pr_2NEt, THF, 23 °C, 2 h, then **25**, DMAP, benzene, 23 °C, 1 h; (b) TFA, 23 °C, 2 h, then 2,4,6-(Cl_3)PhCOCl, *i*Pr_2NEt, DMAP, THF, 23 °C, 1 h, then benzene, 23 °C, 12 h; (c) $Me_2C(O)_2$, CH_2Cl_2, −30 to 23 °C, 12 h

in 91% yield by reaction with DCC and DMAP in DCM at room temperature for 12 h. The resulting diester was debenzylated by hydrogenation in the presence of 10% Pd/C in EtOAc and fragment **33** was obtained in 97% yield.

With all essential pieces in hand, the macrolides of cryptophycin B and arenastatin A were constructed by linking fragment **25** with fragments **32** and **33**, respectively, and subsequent macrolactamization between the D-tyrosine and β-amino acid segments. As summarized in Scheme 4, acid **32** was treated with 2,4,6-trichlorobenzoyl chloride and *i*Pr_2NEt in THF at room temperature for 2 h to form the corresponding anhydride. After evaporation of the solvent, the anhydride was treated with fragment **25** and DMAP in benzene at ambient temperature for 1 h. Cryptophycin B precursor **34** was obtained in 84% yield. Treatment of **34** with a solution of 50% TFA in DCM for 1 h rendered the free amine (crude NMR), while the *tert*-butyl ester was inert to these conditions. Therefore, **34** was converted into cryptophycin D (**4**) by *tert*-butyl removal with neat TFA at room temperature for 2 h (crude NMR of the concentrated mixture showed loss of both *tert*-butyl groups) and subsequent macrolactamization under Yamaguchi conditions by treatment of the resulting amino acid with 2,4,6-trichlorobenzoyl chloride, *i*Pr_2NEt and DMAP in benzene at room temperature for 1 h. This one-pot procedure afforded macrolide **4** in 74% yield. Spectroscopic and analytical data are in agreement with those reported {$[\alpha]_D^{23}$ = +36.2 (*c* = 0.72, MeOH); ref.[2] $[\alpha]_D^{23}$ = +36.7 (*c* = 1.93, MeOH)}. The same coupling-deprotection-macrocyclization procedure was applied to fragment **33** to produce protected amino acid **35** and deoxyarenastatin A (**36**) in 80% and 81% yield, respectively.

The epoxidation of the styryl double bond concluded the syntheses of cryptophycin B and arenastatin A. The most reliable and reproducable procedure previously published is the epoxidation with dimethyldioxirane.[21,29] Accordingly, the treatment of cryptophycin D (**4**) with dimethydioxirane[47] at −30 °C for 2 h and room temperature for 10 h furnished cryptophycin B (**2**) in 87% yield as a 3:1 mixture of diastereomers (determined by ^1H NMR) (Scheme 4). Since both isomers could not be separated by flash column chromatography, clean separation of the major epoxide was accomplished by reversed phase HPLC (YMC-PACK ODS-AQ 5S 120Å 4.6 × 250 mm, MeOH/H_2O, 3:1, 1 mL/min).[33] Retention times for **2** and its minor isomer were 31.58 and 37.20 min, respectively. Unfortunately, the minor isomer could not be obtained in pure form. Spectroscopic and analytical data for cryptophycin B are in agreement with those reported {$[\alpha]_D^{23}$ = +20.6 (*c* = 0.24, MeOH); ref.[2] $[\alpha]_D^{23}$ = +20.4 (*c* = 0.54, MeOH)}. Epoxidation of deoxyarenastatin A (**36**) under the same conditions afforded arenastatin A (**5**) in 75% yield as a 3:1 mixture of diastereomers (determined by ^1H NMR). Spectroscopic and analytical data for arenastatin A are in agreement with

those reported {$[\alpha]_D^{23} = +48.1$ ($c = 0.09$, $CHCl_3$); ref.[33] $[\alpha]_D^{23} = +48.7$ ($c = 0.87$, $CHCl_3$)}. In addition to the utilized epoxidation procedure, several other epoxidation protocols were tried. Shi's fructose-based dioxirane,[48−50] *N*-sulfonyloxaziridine,[51,52] and Jacobsen's catalyst[53] did not give a higher selectivity or any epoxy product at all. On the other hand, methyl(trifluoromethyl)dioxirane did epoxidize the olefin with comparable selectivities.[54,55]

The stereochemical outcome of the epoxidation with dimethyldioxirane could be rationalized according to Figure 3. The oxygen atom transfer from dimethyldioxirane to the olefin takes places by means of perpendicular approach of dimethyldioxirane.[56] This orientation of the transition state benefits from a stabilizing interaction of an oxygen lone pair with the π* orbital of the olefin. The sterically demanding isobutyl group is shielding the α-face of the double bond. This would favour an oxygen transfer from the β-face.

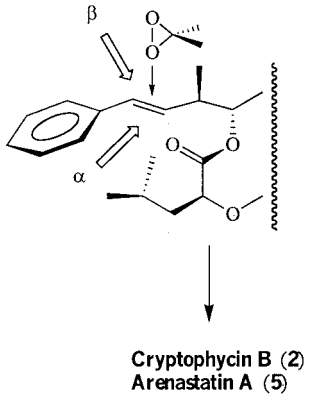


Figure 3. Stereochemical model for epoxidation

Conclusion

In summary, high yielding total syntheses of the antitumor agents cryptophycin B and arenastatin A have been accomplished in a convergent manner. This is the first total synthesis of cryptophycin B. The syntheses utilized a highly stereoselective ester-derived *syn*-aldol reaction to control the absolute stereochemistry of the octadienoic acid fragment. Selective cleavage of a benzyl ether by use of a Lewis acid was achieved in presence of an acid-sensitive silyl ether group. The assembly of the macrolide fragments was accomplished by Yamaguchi- and Steglich-type esterification and amidation reactions. Ring-closing to the macrolides was performed by Yamaguchi lactamization. A stereoselective epoxidation installed the epoxy moieties of cryptophycin B and arenastatin A. Starting from **13** the overall yields for cryptophycin B and arenastatin A were 20 and 18%, respectively. The present synthesis provides convenient access to structural analogues of cryptophycins which are in great demand, considering the high clinical potential of cryptophycins.

Experimental Section

General: Melting points are uncorrected. Anhydrous solvents and reagents were obtained as follows: tetrahydrofuran by distillation from sodium and benzophenone, dichloromethane by distillation from CaH_2, triethylamine by distillation from CaH_2. All other solvents were of HPLC grade. Flash column chromatography was performed with Whatman 240−400 mesh silica gel under low pressure (5−10 psi). Thin-layer chromatography (TLC) was carried out with E. Merck silica gel 60 F-254 plates. All starting materials are commercially available from Sigma−Aldrich®.

(3*E*,1′*R*,2′*S*)-1′-[(*p*-Tolylsulfonyl)amino]indan-2′-yl 4-Phenylbut-3-enoate (14): 13 (2.69 g, 17.5 mmol) was dissolved in DCM (200 mL) and the solution was cooled to 0 °C. *p*-Toluenesulfonyl chloride (3.34 g, 17.5 mmol) and DMAP (4.27 g, 35.0 mmol) were added and the mixture was stirred at room temperature for 1 h. (3*E*)-4-Phenylbut-3-enoic acid (2.20 mL, 17.5 mmol) and EDCI (3.36 g, 17.5 mmol) were added and after stirring at room temperature for 6 h, the reaction mixture was successively washed with saturated aqueous NH_4Cl and $NaHCO_3$. Drying of the organic layer with Na_2SO_4 and concentration in vacuo yielded **14** (7.75 g, 98%) as a white solid. M.p. 105 °C. $[\alpha]_D^{23} = +3.82$ ($c = 4.30$, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.84 (d, ^3J = 8.5 Hz, 2 H), 7.36−7.20 (m, 11 H), 6.44 (d, ^3J = 16.0 Hz, 1 H), 6.19 (dt, ^3J = 16.0, ^3J = 7.2 Hz, 1 H), 5.60 (d, ^3J = 10.5 Hz, 1 H), 5.18 (ddd, 1 H, ^3J = 4.0, ^3J = 4.0, ^3J = 1.5 Hz), 5.05 (dd, ^3J = 10.5, ^3J = 5.0 Hz, 1 H), 3.13 (m, 3 H), 2.96 (d, ^2J = 17.2 Hz, 1 H), 2.43 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 171.0, 144.3, 140.1, 139.0, 138.3, 137.1, 134.1, 130.4, 129.1, 129.0, 128.1, 127.9, 127.3, 126.7, 125.5, 124.8, 121.6, 75.5, 60.0, 38.3, 37.9, 22.0 ppm. IR (film): $\tilde{\nu}$ = 3282 (br. s), 1738 (s), 1598 (w), 1447 (m), 1435 (s), 1335 (s), 1161 (s), 1093 (s) cm^{-1}. HRMS (FAB): *m*/*z* calcd. $C_{26}H_{25}NNaO_4S$ [M + Na^+] 470.1402, found 470.1404. LRMS (FAB): *m*/*z* (%) = 470.0 (52), 329.0 (27), 277.1 (19), 176.1 (100), 154.1 (68), 136.1 (51), 117.1 (29), 76.9 (25).

(2*R*,3*E*,1′*S*,1′′*R*,2′′*S*)-1′′-[(*p*-Tolylsulfonyl)amino]indan-2′′-yl 2-[3′-(Benzyloxy)-1′-hydroxypropyl]-4-phenylbut-3-enoate (15): To a solution of **14** (2.00 g, 4.47 mmol) in DCM (50 mL) was added $TiCl_4$ (1.0 M in DCM, 4.50 mL, 4.47 mmol) at 0 °C. After stirring for 15 min, *i*Pr_2NEt (2.57 mL, 14.7 mmol) was added dropwise at 0 °C and the resulting mixture was stirred at room temperature for 1 h. It was cooled to −78 °C and $TiCl_4$ (1.0 M in DCM, 8.10 mL, 8.04 mmol) was added at once. Subsequently, 3-(benzyloxy)propionaldehyde (1.25 mL, 8.04 mmol) was added dropwise over a period of 5 min. After stirring at −78 °C for 20 min, the reaction was quenched with saturated aqueous NH_4Cl and the organic layer was dried with Na_2SO_4. Concentration in vacuo (crude NMR showed > 99% *de*) and chromatographic purification (20% EtOAc in hexane) yielded **15** (2.69 g, 98%) as a white solid. M.p. 172 °C. $[\alpha]_D^{23} = +32.5$ ($c = 2.83$, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.81 (d, ^3J = 7.5 Hz, 2 H), 7.38−7.19 (m, 16 H), 6.47 (d, ^3J = 16.0 Hz, 1 H), 6.44 (d, ^3J = 10.0 Hz, 1 H), 6.25 (dd, ^3J = 16.0, ^3J = 9.5 Hz, 1 H), 5.40 (dd, ^3J = 4.5, ^3J = 4.5 Hz, 1 H), 5.02 (dd, ^3J = 10.0, ^3J = 5.0 Hz, 1 H), 4.53 (s, 2 H), 4.25 (dd, ^3J = 7.0, ^3J = 3.7 Hz, 1 H), 3.65 (m, 3 H), 3.19 (dd, ^3J = 10.0, ^3J = 4.0 Hz, 1 H), 3.11 (dd, ^2J = 17.0, ^3J = 4.5 Hz, 1 H), 2.94 (d, ^2J = 17.0 Hz, 1 H), 2.43 (s, 3 H), 1.82 (m, 1 H), 1.68 (m, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 172.0, 143.9, 140.6, 138.9, 138.6, 138.2, 136.9, 135.1, 130.2, 129.1, 129.0, 128.9, 128.8, 128.4, 128.3, 127.8, 127.4, 126.9, 125.3, 124.9, 123.2, 76.0, 73.8, 72.2, 68.7, 60.3, 56.2, 37.7, 34.6, 22.0 ppm. IR (film): $\tilde{\nu}$ = 3487 (br. s), 3274 (br. s), 3060 (m), 3028 (m), 2922 (m), 2867 (m), 1733 (s), 1598 (w), 1451 (s),

1335 (s), 1160 (s), 1119 (w), 1094 (m), 1032 (m), 972 (m), 814 (m), 748 (s) cm^{-1}. HRMS (FAB): *m/z* calcd. $C_{36}H_{37}NNaO_6S$ [M + Na^+] 634.2239, found 634.2224. LRMS (FAB): *m/z* (%) = 634.2 (50), 329.1 (36), 176.1 (100), 154.0 (58), 136.1 (42), 91.1 (49).

(3*S*,4*R*,5*E*)-1-(Benzyloxy)-4-methyl-6-phenylhex-5-en-3-ol (16): To a solution of **15** (2.62 g, 4.28 mmol) in THF (40 mL) at 0 °C was added LAH (0.34 g, 8.56 mmol). The reaction mixture was stirred for 1 h and aqueous $NaHSO_4$ (2.5 M) was added until the solution turned clear. The organic layer was decanted and the aqueous phase was extracted once again with diethyl ether. The combined ether phases were dried with Na_2SO_4, concentrated in vacuo and the residue was chromatographically purified (30% EtOAc in hexane) to yield (2*S*,3*S*)-5-(benzyloxy)-2-[(*E*)-styryl]pentane-1,3-diol (1.23 g, 92%) as a white solid. M.p. 69 °C. $[\alpha]_D^{23}$ = +12.7 (*c* = 0.55, CH_2Cl_2). ^1H NMR ($CDCl_3$, 500 MHz): δ = 7.44−7.33 (m, 10 H), 6.52 (d, ^3J = 16.0 Hz, 1 H), 6.35 (dd, ^3J = 16.0, ^3J = 9.5 Hz, 1 H), 4.54 (s, 2 H), 4.19 (d, ^3J = 10.5 Hz, 1 H), 3.89 (dd, ^3J = 11.0, ^3J = 7.0 Hz, 1 H), 3.82 (dd, ^3J = 11.0, ^3J = 6.0 Hz, 1 H), 3.74 (m, 1 H), 3.70 (m, 1 H), 3.58 (br. s, 2 H), 2.47 (m, 1 H), 1.93 (m, 1 H), 1.73 (m, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 138.4, 137.6, 133.9, 129.0, 128.9, 128.2, 128.1, 127.8, 127.0, 126.7, 73.7, 72.4, 69.4, 65.0, 51.1, 35.0 ppm. IR (film): $\tilde{\nu}$ = 3393 (br. s), 3060 (w), 3027 (w), 2923 (m), 2869 (m), 1599 (w), 1452 (m), 1364 (m), 1093 (s), 1028 (m), 971 (m), 749 (s) cm^{-1}. HRMS (CI): *m/z* calcd. $C_{20}H_{25}O_3$ [M + H^+] 313.1804, found 313.1809. LRMS (CI): *m/z* (%) = 330.2 (75), 313.2 (100). Phenyllithium (1.8 M in cyclohexane/diethyl ether, 3.90 mL, 7.04 mmol) was added dropwise to a solution of (2*S*,3*S*)-5-(benzyloxy)-2-[(*E*)-styryl]pentane-1,3-diol (2.20 g, 7.04 mmol) in THF (60 mL) at −78 °C. The reaction mixture was stirred at −78 °C for 30 min and TsCl (1.34 g, 7.04 mmol) was added in one portion. The reaction mixture was allowed to warm to −20 °C over a period of 30 min and was subsequently treated with LAH (0.85 g, 21.1 mmol). After 20 min, the reaction was quenched and the mixture washed with saturated aqueous NH_4Cl, dried with Na_2SO_4 and concentrated in vacuo. The residue was chromatographically purified (20% EtOAc in hexane) to give **16** (2.01 g, 96%) as a colorless oil. $[\alpha]_D^{23}$ = +25.2 (*c* = 6.61, CH_2Cl_2). ^1H NMR ($CDCl_3$, 500 MHz): δ = 7.41−7.20 (m, 10 H), 6.47 (d, ^3J = 16.0 Hz, 1 H), 6.27 (dd, ^3J = 16.0, ^3J = 8.5 Hz, 1 H), 4.57 (s, 2 H), 3.84−3.70 (m, 3 H), 2.70 (br. s, 1 H), 2.45 (dd, ^3J = 6.5, ^3J = 1.5 Hz, 1 H), 1.83 (m, 2 H), 1.19 (d, ^3J = 6.5 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 138.4, 137.9, 132.5, 131.2, 128.9, 128.2, 128.1, 127.5, 126.6, 126.7, 75.1, 73.8, 69.7, 43.9, 34.3, 16.9 ppm. IR (film): $\tilde{\nu}$ = 3448 (br. s), 3060 (m), 3027 (m), 2961 (m), 2926 (m), 2869 (m), 1595 (m), 1495 (m), 1453 (s), 1364 (m), 1095 (s), 1028 (m), 970 (m), 748 (s) cm^{-1}. HRMS (CI): *m/z* calcd. $C_{20}H_{25}O_2$ [M + H^+] 297.1855, found 297.1846. LRMS (CI): *m/z* (%) = 314.2 (100), 297.3 (81).

(1*S*,2*R*,3*E*)-({1-[2′-(Benzyloxy)ethyl]-2-methyl-4-phenylbut-3-enyl}oxy)triisopropylsilane (17): To a solution of **16** (1.60 g, 5.40 mmol) and 2,6-lutidine (1.26 mL, 10.8 mmol) in DCM (40 mL) was added TIPSOTf (2.18 mL, 8.10 mmol). The resulting solution was stirred at room temperature for 20 min, concentrated in vacuo and chromatographically purified (10% EtOAc in hexanes) to furnish **17** (2.42 g, 99%) as a colorless oil. $[\alpha]_D^{23}$ = +41.8 (*c* = 3.20, CH_2Cl_2). ^1H NMR ($CDCl_3$, 500 MHz): δ = 7.42−7.35 (m, 9 H), 7.28 (t, ^3J = 7.1 Hz, 1 H), 6.44 (d, ^3J = 16.0 Hz, 1 H), 6.30 (dd, ^3J = 16.0, ^3J = 7.5 Hz, 1 H), 4.56 (q, ^3J = 12.5 Hz, 2 H), 4.15 (m, 1 H), 3.64 (t, ^3J = 7.0 Hz, 2 H), 2.63 (m, 1 H), 1.90 (m, 2 H), 1.24 (d, ^3J = 7.0 Hz, 3 H), 1.18 (s, 21 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 139.0, 138.2, 133.0, 130.3, 128.9, 128.8, 128.1, 127.9, 127.4, 126.5, 73.9, 73.4, 67.9, 43.3, 34.4, 18.8, 15.6, 13.4 ppm. IR (film): $\tilde{\nu}$ = 3060 (m), 3027 (m), 2943 (s), 2866 (s), 1596 (m), 1493 (m), 1463 (s), 1365 (m), 1263 (m), 1104 (s), 1068 (m), 968 (m), 883 (m), 747 (m) cm^{-1}. HRMS (FAB): *m/z* calcd. $C_{29}H_{44}O_2NaSi$ [M + Na^+] 475.3008, found 475.2994. LRMS (FAB): *m/z* (%) = 321.3 (20), 215.2 (42), 157.2 (60), 131.2 (78), 115.2 (72), 91.1 (100), 73.0 (86), 60.9 (67).

(3*R*,4*R*,5*E*)-3-Bromo-4-methyl-6-phenylhex-5-en-1-ol (18): A solution of **17** (30.0 mg, 66.3 μmol) in DCM (2 mL) was cooled to 0 °C. BBr_3 (1.0 M in DCM, 100 μL, 99.5 μmol) was added dropwise and after 5 min of stirring at 0 °C, the reaction was quenched and the mixture washed with saturated aqueous $NaHCO_3$, dried with Na_2SO_4 and concentrated in vacuo. Chromatographic purification (10% EtOAc in hexanes) of the residue furnished **18** (8.0 mg, 45%) as a colorless oil. $[\alpha]_D^{23}$ = +40.5 (*c* = 0.85, CH_2Cl_2). ^1H NMR ($CDCl_3$, 500 MHz): δ = 7.40 (d, ^3J = 9.0 Hz, 2 H), 7.33 (dd, ^3J = 10.5, ^3J = 9.0 Hz, 2 H), 7.26 (d, ^3J = 8.0 Hz, 1 H), 6.50 (d, ^3J = 20.0 Hz, 1 H), 6.13 (dd, ^3J = 20.0, ^3J = 11.0 Hz, 1 H), 4.32 (dtd, 1 H, ^3J = 8.5, ^3J = 8.5, ^3J = 3.5 Hz), 3.76 (m, 1 H), 3.67 (m, 1 H), 2.50 (qd, ^3J = 8.5, ^3J = 3.5 Hz, 1 H), 1.90−1.84 (m, 2 H), 1.70 (d, ^3J = 8.5 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 137.3, 134.0, 129.2, 129.0, 128.0, 126.7, 60.8, 56.8, 47.4, 37.1, 24.7 ppm.

(3*S*,4*R*,5*E*)-4-Methyl-6-phenyl-3-[(triisopropylsilanyl)oxy]hex-5-enal (19): To a solution of **17** (1.30 g, 2.87 mmol) in DCM (50 mL) was added K_2CO_3 (1.00 g). The resulting mixture was stirred at room temperature for 20 min and was then cooled to 0 °C. BBr_3 (1.0 M in DCM, 3.12 mL, 3.12 mmol) was added dropwise and after 5 min of stirring at 0 °C, the reaction was quenched and the mixture washed with saturated aqueous $NaHCO_3$, dried with Na_2SO_4 and concentrated in vacuo. Chromatographic purification (10% EtOAc in hexanes) of the residue furnished (3*S*,4*R*,5*E*)-4-methyl-6-phenyl-3-[(triisopropylsilanyl)oxy]hex-5-en-1-ol (865 mg, 83%) as a colorless oil. $[\alpha]_D^{23}$ = +33.3 (*c* = 0.63, CH_2Cl_2). ^1H NMR ($CDCl_3$, 500 MHz): δ = 7.37 (d, ^3J = 8.5 Hz, 2 H), 7.33 (dd, ^3J = 10.5, ^3J = 9.0 Hz, 2 H), 7.23 (dd, ^3J = 8.5, ^3J = 8.5 Hz, 1 H), 6.42 (d, ^3J = 16.0 Hz, 1 H), 6.21 (dd, ^3J = 16.0, ^3J = 7.5 Hz, 1 H), 4.12 (m, 1 H), 3.80 (t, ^3J = 6.5 Hz, 2 H), 2.65 (m, 1 H), 1.79 (m, 2 H), 1.19 (d, ^3J = 7.0 Hz, 3 H), 1.13 (s, 21 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 138.0, 132.9, 130.4, 128.9, 127.5, 126.4, 75.0, 61.0, 43.2, 35.9, 18.6, 14.9, 13.4 ppm. IR (film): $\tilde{\nu}$ = 3352 (br. s), 3025 (m), 2943 (s), 2866 (s), 1600 (w), 1463 (s), 1383 (s), 1246 (m), 1102 (s), 1061 (s), 968 (m), 883 (s), 748 (m) cm^{-1}. HRMS (CI): *m/z* calcd. $C_{22}H_{39}O_2Si$ [M + H^+] 363.2719, found 363.2693. LRMS (CI): *m/z* (%) = 363.4 (43), 206.2 (52), 189.2 (100), 171.2 (30). To a solution of (3*S*,4*R*,5*E*)-4-methyl-6-phenyl-3-[(triisopropylsilanyl)oxy]hex-5-en-1-ol (800 mg, 2.21 mmol) in DCM (100 mL) was added molecular sieves (4 Å) (2.50 g). The resulting mixture was stirred at room temperature for 10 min and PCC (713 mg, 3.31 mmol) was added portionwise. After 10 min of stirring at room temperature, the reaction mixture was filtered through a pad of Celite© and the resulting filtrate was concentrated in vacuo. Chromatographic purification (50% diethyl ether in hexanes) of the residue afforded **19** (781 mg, 98%) as a colorless oil. $[\alpha]_D^{23}$ = +27.1 (*c* = 1.62, CH_2Cl_2). ^1H NMR ($CDCl_3$, 500 MHz): δ = 9.85 (t, ^3J = 2.0 Hz, 1 H), 7.38−7.32 (m, 4 H), 7.26 (dd, ^3J = 8.5, ^3J = 8.5 Hz, 1 H), 6.42 (d, ^3J = 16.0 Hz, 1 H), 6.15 (dd, ^3J = 16.0, ^3J = 7.5 Hz, 1 H), 4.50 (td, ^3J = 6.0, ^3J = 4.0 Hz, 1 H), 2.66 (m, 1 H), 2.61 (td, ^3J = 4.0, ^3J = 2.0 Hz, 2 H), 1.20 (d, ^3J = 7.0 Hz, 3 H), 1.11 (s, 21 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 202.3, 137.7, 131.8, 131.3, 129.0, 127.7, 126.5, 72.0, 48.4, 43.8, 18.6, 14.8, 13.1 ppm. IR (film): $\tilde{\nu}$ = 3027 (w), 2943 (s), 2867 (s), 1725 (s), 1601 (w), 1463 (s), 1384 (m), 1284 (m), 1100 (s), 1068 (s), 883 (s), 749 (m)

cm^{-1}. HRMS (CI): *m/z* calcd. $C_{22}H_{37}O_2Si$ [M + H^+] 361.2563, found 361.2570. LRMS (CI): *m/z* (%) = 393.4 (100) [M + Na^+], 309.2 (83), 192.3 (62), 75.1 (74).

(2*E*,5*S*,6*R*,7*E*)-Ethyl 6-Methyl-8-phenyl-5-[(triisopropylsilanyl)oxy]-octa-2,7-dienoate (20): To a dispersion of NaH (60% dispersion in mineral oil, 306 mg, 12.8 mmol) in THF (15 mL) was added triethyl phosphonoacetate (633 μL, 3.19 mmol) and the resulting mixture was stirred at room temperature for 10 min. Then, the reaction mixture was cooled to 0 °C and **19** (1.15 g, 3.19 mmol) in THF (10 mL) was added. After stirring at 0 °C for 10 min, the reaction was quenched with saturated aqueous NH_4Cl and the organic phase was dried with Na_2SO_4. Concentration in vacuo and chromatographic purification (5% EtOAc in hexane) of the residue yielded **20** (1.27 mg, 92%) as a single isomer by ^1H NMR and as colorless oil. $[\alpha]_D^{23}$ = +73.7 (*c* = 2.78, CH_2Cl_2). ^1H NMR ($CDCl_3$, 500 MHz): δ = 7.39 (d, ^3J = 7.5 Hz, 2 H), 7.34 (dd, ^3J = 8.0, ^3J = 7.5 Hz, 2 H), 7.26 (dd, ^3J = 8.0, ^3J = 8.0 Hz, 1 H), 7.03 (dt, ^3J = 16.0, ^3J = 8.0 Hz, 1 H), 6.43 (d, ^3J = 16.0 Hz, 1 H), 6.24 (dd, ^3J = 16.0, ^3J = 7.5 Hz, 1 H), 5.89 (d, ^3J = 16.0 Hz, 1 H), 4.22 (q, ^3J = 7.0 Hz, 2 H), 4.04 (m, 1 H), 2.59 (m, 1 H), 2.47 (m, 2 H), 1.31 (t, ^3J = 7.0 Hz, 3 H), 1.21 (d, ^3J = 7.0 Hz, 3 H), 1.14 (s, 21 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 166.8, 146.4, 138.0, 132.2, 130.9, 128.9, 127.5, 126.5, 123.7, 75.9, 60.6, 43.3, 38.0, 18.7, 16.2, 14.7, 13.3 ppm. IR (film): $\tilde{\nu}$ = 3026 (w), 2943 (s), 2867 (s), 1723 (s), 1655 (m), 1600 (w), 1463 (s), 1367 (m), 1264 (m), 1169 (m), 1101 (s), 1045 (s), 882 (s), 747 (m) cm^{-1}. HRMS (FAB): *m/z* calcd. $C_{26}H_{42}O_3NaSi$ [M + Na^+] 453.2801, found 453.2783. LRMS (FAB): *m/z* (%) = 430.3 (10), 387.3 (39), 317.3 (33), 299.3 (95), 131.2 (65), 73.0 (75), 59.0 (100).

(2*E*,5*S*,6*R*,7*E*)-6-Methyl-8-phenyl-5-[(triisopropylsilanyl)oxy]octa-2,7-dienonic Acid (21). From Ester 20: A mixture of **20** (1.10 g, 2.55 mmol) and $LiOH·H_2O$ (320 mg, 7.66 mmol) in EtOH (20 mL) and H_2O (20 mL) was vigorously stirred at room temperature for 2 h. After the reaction was quenched with saturated aqueous NH_4Cl, the water layer was acidified with concentrated HCl (pH = 3) and extracted with DCM. The organic layer was dried with Na_2SO_4, concentrated in vacuo and chromatographically purified (25% EtOAc in hexane) to yield **21** (954 mg, 94%) as a white solid. **From Aldehyde 19:** A solution of **19** (160 mg, 0.42 mmol) and malonic acid (44.0 mg, 0.42 mmol) in Et_3N (0.5 mL) and benzene (3 mL) was heated under reflux for 4 h. The reaction mixture was taken up with diethyl ether, washed with 20% aqueous HCl and subsequently dried with Na_2SO_4. Concentration in vacuo and chromatographic purification yielded **21** (60 mg, 33%) as a white solid. M.p. 88 °C. $[\alpha]_D^{23}$ = +83.8 (*c* = 7.20, CH_2Cl_2). ^1H NMR ($CDCl_3$, 500 MHz): δ = 7.39 (d, ^3J = 7.5 Hz, 2 H), 7.34 (dd, ^3J = 8.0, ^3J = 7.5 Hz, 2 H), 7.26 (dd, ^3J = 8.0, ^3J = 8.0 Hz, 1 H), 7.15 (dt, ^3J = 16.0, ^3J = 8.0 Hz, 1 H), 6.43 (d, ^3J = 16.0 Hz, 1 H), 6.23 (dd, ^3J = 16.0, ^3J = 7.5 Hz, 1 H), 5.90 (d, ^3J = 16.0 Hz, 1 H), 4.05 (m, 1 H), 2.57 (m, 1 H), 2.49 (m, 2 H), 1.20 (d, ^3J = 7.0 Hz, 3 H), 1.14 (s, 21 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 172.2, 149.5, 137.9, 132.1, 131.0, 128.9, 127.5, 126.5, 123.0, 75.8, 43.4, 38.1, 18.6, 16.2, 13.2 ppm. IR (film): $\tilde{\nu}$ = 3025 (w), 2943 (s), 2866 (s), 1698 (s), 1652 (s), 1463 (m), 1420 (m), 1103 (s), 882 (s), 747 (m) cm^{-1}. HRMS (FAB): *m/z* calcd. $C_{24}H_{38}NaO_3Si$ [M + Na^+] 425.2488, found 425.2502. LRMS (FAB): *m/z* (%) = 447.2 (54), 425.2 (20) [M + Na^+], 131.1 (34), 116.1 (38), 87.0 (50), 73.5 (84), 70.2 (100).

(*R*)-*tert*-Butyl 2-amino-3-(4-methoxyphenyl)propionate (23): A mixture of **22** (1.00 g, 3.17 mmol), Me_2SO_4 (1.38 mL, 14.3 mmol), NaOH (960 mg, 23.8 mmol), EtOH (50 mL) and H_2O (1 mL) was vigorously stirred under reflux for 3 h. After the reaction was quenched with saturated aqueous NH_4Cl, the water layer was acidified with concentrated HCl (pH = 3) and extracted with diethyl ether. The organic layer was washed with brine, dried with Na_2SO_4 and concentrated in vacuo to yield (*R*)-2-{[(benzyloxy)-carbonyl]amino}-3-(4-methoxyphenyl)propionic acid (950 mg, 91%) as a white solid. M.p. 111−112 °C. $[\alpha]_D^{23}$ = −37.8 (*c* = 1.66, $CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz): δ = 7.38 (m, 5 H), 7.09 (d, ^3J = 8.5 Hz, 2 H), 6.85 (d, ^3J = 8.5 Hz, 2 H), 5.22 (d, ^3J = 8.0 Hz, 1 H), 5.13 (d, ^3J = 6.0 Hz, 2 H), 4.68 (dd, ^3J = 8.5, ^3J = 6.0 Hz, 1 H), 3.80 (s, 3 H), 3.17 (dd, ^2J = 14.0, ^3J = 5.5 Hz, 1 H), 3.09 (dd, ^2J = 14.0, ^3J = 6.0 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 176.6, 159.2, 156.3, 136.5, 130.8, 129.0, 128.7, 128.6, 127.7, 114.5, 67.6, 55.6, 55.1, 37.3 ppm. IR (film): $\tilde{\nu}$ = 3330 (br. s), 1715 (s), 1514 (s), 1248 (s), 1057 (m), 1036 (m), 738 (m) cm^{-1}. HRMS (CI): *m/z* calcd. $C_{18}H_{20}NO_5$ [M + H^+] 330.1341, found 330.1351. LRMS (CI): *m/z* (%) = 347.2 (100) [M + NH_4^+], 330.2 (40) [M + H^+], 286.2 (43), 196.1 (23). To a solution of (*R*)-2-{[(benzyloxy)carbonyl]amino}-3-(4-methoxyphenyl)propionic acid (1.27 g, 3.87 mmol) in THF (25 mL) were successively added iPr$_2$NEt (674 μL, 3.87 mmol) and 2,4,6-trichlorobenzyl chloride (604 μL, 3.87 mmol). After 30 min of stirring, the solvent was evaporated and the residue was dissolved in toluene (20 mL). tBuOH (740 μL, 7.74 mmol) and DMAP (1.89 g, 15.5 mmol) were added and the mixture was stirred for a further 3 h. The reaction mixture was entirely transferred onto a column and chromatographically purified (25% EtOAc in hexane) to yield (*R*)-*tert*-butyl 2-{[(benzyloxy)carbonyl]amino}-3-(4-methoxyphenyl)propionate (946 mg, 64%) as a colorless oil. $[\alpha]_D^{23}$ = −17.9 (*c* = 9.70, CH_2Cl_2). ^1H NMR ($CDCl_3$, 500 MHz): δ = 7.38 (m, 5 H), 7.09 (d, ^3J = 8.5 Hz, 2 H), 6.83 (d, ^3J = 8.5 Hz, 2 H), 5.26 (d, ^3J = 8.0 Hz, 1 H), 5.13 (d, ^3J = 6.0 Hz, 2 H), 4.52 (dd, ^3J = 8.5, ^3J = 6.5 Hz, 1 H), 3.81 (s, 3 H), 3.06 (t, ^3J = 5.0 Hz, 2 H), 1.44 (s, 9 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 171.1, 159.0, 156.0, 136.8, 130.9, 128.9, 128.9, 128.5, 128.4, 114.2, 82.6, 67.2, 55.7, 55.6, 37.9, 28.4 ppm. IR (film): $\tilde{\nu}$ = 3343 (br. s), 2977 (m), 2934 (w), 2835 (w), 1723 (s), 1613 (m), 1513 (s), 1368 (m), 1249 (s), 1155 (s), 1056 (m), 1038 (m), 740 (m) cm^{-1}. HRMS (FAB): *m/z* calcd. $C_{22}H_{27}NNaO_5$ [M + Na^+] 408.1787, found 408.1796. LRMS (FAB): *m/z* (%) = 386.2 (14) [M + H^+], 330.1 (81), 286.1 (95), 234.1 (82), 178.1 (28), 154.1 (34), 121.1 (79), 91.0 (100), 60.2 (50). A mixture of (*R*)-*tert*-butyl 2-{[(benzyloxy)carbonyl]amino}-3-(4-methoxyphenyl)propionate (640 mg, 1.66 mmol), 5% Pd/C (20 mg) and MeOH (20 mL) was stirred for 2 h under H_2 and filtered through a pad of Celite®. Concentration of the filtrate in vacuo yielded **23** (406 mg, 95%) as a white solid. M.p. 176 °C (gas emission and formation of new solid). $[\alpha]_D^{23}$ = +71.3 (*c* = 0.08, $CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz): δ = 7.14 (d, ^3J = 8.5 Hz, 2 H), 6.86 (d, ^3J = 8.5 Hz, 2 H), 3.80 (s, 3 H), 3.58 (dd, ^3J = 7.5, ^3J = 5.5 Hz, 1 H), 3.00 (dd, ^2J = 14.0, ^3J = 5.5 Hz, 1 H), 2.81 (dd, ^2J = 14.0, ^3J = 8.0 Hz, 1 H), 1.68 (br. s, 2 H), 1.46 (s, 9 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 174.7, 158.8, 130.8, 129.8, 114.3, 81.6, 56.8, 55.7, 40.6, 28.4 ppm. HRMS (CI): *m/z* calcd. $C_{14}H_{22}NO_3$ [M + H^+] 252.1600, found 252.1598. LRMS (FAB): *m/z* = 252.3 (100) [M + H^+], 196.1 (35).

(2*R*,2′*E*,5′*S*,6′*R*,7′*E*)-*tert*-Butyl 3-(4-Methoxyphenyl)-2-({6′-methyl-8′-phenyl-5′-[(triisopropylsilanyl)oxy]octa-2′,7′-dienoyl}amino)-propionate (24): A solution of **21** (700 mg, 1.74 mmol), **23** (437 mg, 1.74 mmol), DMAP (105 mg, 0.87 mmol) and EDCI (334 mg, 1.74 mmol) was stirred at room temperature for 12 h. The reaction mixture was quenched with saturated aqueous NH_4Cl and the organic phase was dried with Na_2SO_4. Concentration in vacuo and chromatographic purification of the residue (15% EtOAc in hexane) yielded **24** (931 mg, 83%) as a white solid. M.p. 64−65 °C. $[\alpha]_D^{23}$ = +29.9 (*c* = 0.87, CH_2Cl_2). ^1H NMR ($CDCl_3$, 400 MHz): δ =

7.34−7.26 (m, 4 H), 7.22 (dd, ^3J = 8.0, ^3J = 8.0 Hz, 1 H), 7.04 (d, ^3J = 8.4 Hz, 2 H), 6.83 (dt, ^3J = 16.0, ^3J = 8.0 Hz, 1 H), 6.80 (d, ^3J = 8.4 Hz, 2 H), 6.36 (d, ^3J = 16.0 Hz, 1 H), 6.22 (dd, ^3J = 16.0, ^3J = 8.0 Hz, 1 H), 5.87 (d, ^3J = 7.6 Hz, 1 H), 5.78 (d, ^3J = 16.0 Hz, 1 H), 4.80 (ddd, 1 H, ^3J = 5.6, ^3J = 4.0, ^3J = 1.6 Hz), 3.96 (m, 1 H), 3.77 (s, 3 H), 3.07 (d, ^3J = 5.6 Hz, 1 H), 2.51 (qdd, 1 H, ^3J = 7.2, ^3J = 8.0, ^3J = 7.3, ^3J = 2.6 Hz), 2.40 (m, 2 H), 1.43 (s, 9 H), 1.15 (d, ^3J = 6.8 Hz, 3 H), 1.09 (s, 21 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 171.2, 165.2, 159.0, 142.1, 138.1, 132.3, 131.0, 130.8, 128.9, 128.5, 127.4, 126.5, 125.7, 114.2, 82.8, 76.0, 55.6, 53.9, 42.9, 38.2, 37.5, 28.4, 18.7, 17.1, 13.3 ppm. IR (film): ṽ = 3299 (br. m), 2942 (s), 2866 (s), 1733 (s), 1671 (s), 1513 (s), 1463 (m), 1367 (s), 1249 (s), 1155 (s), 1109 (m), 1036 (s), 882 (m), 749 (m) cm^{-1}. HRMS (FAB): *m/z* calcd. $C_{38}H_{57}NNaO_5Si$ [M + Na^+] 658.3904, found 658.3912. LRMS (FAB): *m/z* (%) = 658.4 (82) [M + Na^+], 602.4 (45), 176.1 (62), 122.1 (53), 116.1 (52), 88.0 (53), 60.9 (100).

(2*R*,2′*E*,5′*S*,6′*R*,7′*E*)-*tert*-Butyl 2-[(5′-Hydroxy-6′-methyl-8′-phenylocta-2′,7′-dienoyl)amino]-3-(4-methoxyphenyl)propionate (25): A solution of **24** (440 mg, 0.69 mmol) and TBAF (690 μL, 0.69 mmol) in THF (30 mL) was stirred at room temperature for 6 h. The reaction mixture was concentration in vacuo, the residue was redissolved in DCM and filtered through a short pad of $MgSO_4$. Evaporation of solvent yielded **25** (329 mg, 99%) as a highly viscous oil. $[\alpha]_D^{23}$ = −13.3 (*c* = 0.15, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.37 (d, ^3J = 7.4 Hz, 2 H), 7.31 (dd, ^3J = 7.4, ^3J = 7.4 Hz, 2 H), 7.25 (dd, ^3J = 7.8, ^3J = 7.8 Hz, 1 H), 7.06 (d, ^3J = 8.4 Hz, 2 H), 6.85 (dt, ^3J = 16.0, ^3J = 8.0 Hz, 1 H), 6.80 (d, ^3J = 8.4 Hz, 2 H), 6.48 (d, ^3J = 16.0 Hz, 1 H), 6.12 (dd, ^3J = 16.0, ^3J = 8.0 Hz, 1 H), 5.91 (d, ^3J = 7.2 Hz, 1 H), 5.82 (d, ^3J = 16.0 Hz, 1 H), 4.80 (ddd, 1 H, ^3J = 5.6, ^3J = 4.0, ^3J = 1.6 Hz), 3.77 (s, 3 H), 3.65 (m, 1 H), 3.08 (d, ^3J = 6.6 Hz, 1 H), 2.46−2.33 (m, 3 H), 1.42 (s, 9 H), 1.14 (d, ^3J = 6.8 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 171.1, 165.2, 159.0, 141.7, 137.5, 132.3, 131.4, 131.0, 129.0, 128.5, 127.8, 126.6, 126.3, 114.2, 82.8, 74.2, 55.6, 54.0, 43.6, 37.3, 37.5, 28.4, 17.3 ppm. IR (film): ṽ = 3340 (br. s), 2960 (m), 2925 (s), 2853 (s), 1730 (s), 1670 (s), 1635 (s), 1513 (s), 1457 (m), 1368 (s), 1249 (s), 1154 (s), 1036 (m), 751 (w) cm^{-1}. HRMS (FAB): *m/z* calcd. $C_{29}H_{37}NNaO_5$ [M + Na^+] 502.2569, found 502.2558. LRMS (FAB): *m/z* (%) = 446.3 (36), 413.4 (25), 176.1 (100), 91.9 (30), 59.1 (29).

(*S*)-Benzyl 2-Hydroxy-4-methylpentanoate (27):[45] To a solution of **26** (2.77 g, 21.0 mmol) in MeOH (40 mL) and H_2O (8 mL) was added Cs_2CO_3 (3.42 g, 10.5 mmol). After stirring at room temperature for 30 min, the reaction mixture was concentrated to dryness and the residue was redissolved in DMF. The solution was cooled to 0 °C, benzyl bromide (2.5 mL, 20 mmol) was added and the resulting mixture was stirred at room temperature for 12 h. The reaction was quenched with saturated aqueous NH_4Cl, extracted with EtOAc and the organic layer was dried with Na_2SO_4. Evaporation of solvent yielded **27** (4.32 g, quant.) as colorless oil. $[\alpha]_D^{23}$ = −15.5 (*c* = 1.02, $CHCl_3$) {ref.[45] $[\alpha]_D^{23}$ = −15.2 (*c* = 2.96, $CHCl_3$)}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.40 (m, 5 H), 5.24 (s, 2 H), 4.27 (dd, ^3J = 8.0, ^3J = 5.0 Hz, 1 H), 2.62 (br. s, 1 H), 1.92 (m, 1 H), 1.60 (m, 2 H), 0.97 (d, ^3J = 5.5 Hz, 3 H), 0.96 (d, ^3J = 5.5 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 176.2, 135.6, 129.1, 129.0, 128.7, 69.6, 67.7, 43.8, 24.8, 23.7, 22.0 ppm.

(*R*)-Methyl 3-{[(*tert*-Butoxy)carbonyl]amino}-2-methylpropionate (29): To a solution of **28** (2.55 g, 21.6 mmol) in DCM (50 mL) were added TsCl (4.12 g, 21.6 mmol), Et_3N (3.01 mL, 21.6 mmol) and DMAP (1.32 g, 10.8 mmol) at 0 °C. After stirring at room temperature for 1 h, the reaction was quenched with saturated aqueous NH_4Cl and the organic layer was dried with Na_2SO_4. Evaporation of the solvent furnished (*R*)-methyl 2-methyl-3-[(*p*-tolylsulfonyl)oxy]propionate (5.87 g, 99%) as a colorless oil. $[\alpha]_D^{23}$ = −3.75 (*c* = 6.42, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.70 (d, 2 H), 7.28 (d, 2 H), 4.11 (dd, ^3J = 9.3, ^3J = 6.9 Hz, 1 H), 3.98 (dd, ^3J = 9.6, ^3J = 6.3 Hz, 1 H), 3.56 (s, 3 H), 2.73 (dq, ^3J = 6.6, ^3J = 6.0 Hz, 1 H), 2.37 (s, 3 H), 1.10 (d, ^3J = 6.0 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 173.0, 144.9, 132.7, 129.8, 127.9, 70.8, 52.0, 39.2, 21.6, 13.6 ppm. IR (film): ṽ = 2986 (m), 2954 (m), 1741 (s), 1598 (m), 1460 (m), 1363 (s), 1179 (s), 1097 (m), 977 (s), 818 (s) cm^{-1}. HRMS (CI): *m/z* calcd. $C_{12}H_{20}NO_5S$ [M + NH_4^+] 290.1062, found 290.1055. LRMS (CI): *m/z* (%) = 290.2 (100) [M + NH_4^+]. A solution of (*R*)-methyl 2-methyl-3-[(*p*-tolylsulfonyl)oxy]propionate (710 mg, 2.61 mmol) and NaN_3 (190 mg, 2.87 mmol) in DMSO (20 mL) was stirred at room temperature for 6 h. EtOAc (100 mL) and H_2O (100 mL) were added, the organic layer was dried with Na_2SO_4 and concentrated in vacuo. The residue was dissolved in EtOAc (50 mL) and di-*tert*-butyl dicarbonate (0.60 mL, 2.61 mmol) and 10% Pd/C (25 mg) were added. The resulting mixture was stirred under H_2 for 12 h and subsequently filtered through a pad of Celite©. Evaporation of the solvent and chromatographic purification (20% EtOAc in hexane) gave **29** (600 mg, quant.) as a colorless oil. $[\alpha]_D^{23}$ = −17.6 (*c* = 2.74, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 4.90 (br. m, 1 H), 3.60 (s, 3 H), 3.19 (m, 2 H), 2.60 (dq, ^3J = 6.9, ^3J = 6.0 Hz, 1 H), 1.34 (s, 9 H), 1.08 (d, ^3J = 7.2 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 175.7, 156.9, 79.2, 51.8, 42.9, 40.0, 28.3, 14.7 ppm. IR (film): ṽ = 3381 (br. s), 2978 (s), 1716 (s), 1518 (s), 1367 (s), 1250 (s), 1175 (s) cm^{-1}. HRMS (CI): *m/z* calcd. $C_{10}H_{20}NO_4$ [M + H^+] 218.1392, found 218.1385. LRMS (CI): *m/z* (%) = 218.2 (100) [M + H^+], 179.2 (40), 162.1 (81), 118.2 (27).

(*R*)-3-{[(*tert*-Butoxy)carbonyl]amino}-2-methylpropionic Acid (30): A solution of **29** (2.62 g, 12.1 mmol) and $LiOH·H_2O$ (1.50 g, 36.3 mmol) in EtOH (50 mL) was stirred at room temperature for 30 min. The reaction mixture was acidified (pH = 4) with 10% aqueous citric acid and extracted with EtOAc. The organic layer was washed with brine, dried with Na_2SO_4 and concentrated in vacuo to furnish **30** (2.46 g, quant.) as a colorless oil. $[\alpha]_D^{23}$ = −25.5 (*c* = 1.41, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 5.07 (br. m, 1 H), 3.38 (m, 1 H), 3.26 (m, 1 H), 2.70 (m, 1 H), 1.45 (s, 9 H), 1.22 (d, ^3J = 7.5 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 181.4, 156.5, 81.5, 43.1, 40.4, 28.8, 15.0 ppm. IR (film): ṽ = 3380 (br. s), 2979 (s), 1708 (s), 1518 (s), 1368 (m), 1252 (m), 1170 (s) cm^{-1}. HRMS (CI): *m/z* calcd. $C_9H_{18}NO_4$ [M + H^+] 204.1236, found 204.1239. LRMS (CI): *m/z* (%) = 204.2 (35) [M + H^+], 165.2 (40), 148.2 (58), 104.1 (22).

(2*S*,2′*R*)-2-[(3′-{[(*tert*-Butoxy)carbonyl]amino}-2′-methylpropionyl)oxy]-4-methylpentanoic Acid (32): A solution of **27** (2.50 g, 12.1 mmol), **30** (2.46 g, 12.1 mmol), DCC (2.50 g, 12.1 mmol) and DMAP (740 mg, 6.05 mmol) in DCM (50 mL) was stirred at room temperature for 12 h. The reaction was quenched with saturated aqueous NH_4Cl and the organic layer was dried with Na_2SO_4. Evaporation of the solvent and chromatographic purification (10% EtOAc in hexane) afforded (2*S*,2′*R*)-benzyl 2-[(3′-{[(*tert*-butoxy)carbonyl]amino}-2′-methylpropionyl)oxy]-4-methylpentanoate (1.83 g, 91%) as colorless film. $[\alpha]_D^{23}$ = −49.7 (*c* = 1.50, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.35 (m, 5 H), 5.21−5.10 (m, 4 H), 3.43 (ddd, ^2J = 12.0, ^3J = 6.5, ^3J = 5.5 Hz, 1 H), 3.17 (ddd, ^2J = 12.0, ^3J = 6.0, ^3J = 5.5 Hz, 1 H), 2.76 (m, 1 H), 1.82−1.60 (m, 3 H), 1.43 (s, 9 H), 1.17 (d, ^3J = 7.5 Hz, 3 H), 0.94 (d, ^3J = 6.4 Hz, 3 H), 0.91 (d, ^3J = 6.4 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 175.2, 171.1, 156.4, 135.6, 129.0, 128.9, 128.7, 79.7, 71.3, 67.5, 43.5, 40.8, 39.9, 28.8, 25.1, 23.4, 21.9,

14.9 ppm. IR (film): $\tilde{\nu}$ = 3394 (br. s), 2962 (s), 1741 (s), 1718 (s), 1508 (s), 1456 (m), 1367 (m), 1252 (m), 1173 (s) cm^{-1}. HRMS (FAB): *m/z* calcd. $C_{21}H_{32}NNaO_6$ [M + Na^+] 430.2206, found 430.2183. LRMS (FAB): *m/z* (%) = 352.1 (19), 308.1 (85), 130.1 (23), 90.9 (100), 60.2 (32). A mixture of (2*S*,2′*R*)-benzyl 2-[(3′-{[(*tert*-butoxy)carbonyl]amino}-2′-methylpropionyl)oxy]-4-methylpentanoate (2.50 g, 6.13 mmol), 5% Pd/C (200 mg) and EtOAc (40 mL) was stirred for 5 h under H_2 and then filtered through a pad of Celite®. Concentration of the filtrate in vacuo yielded **32** (1.84 g, 95%) as a white solid. M.p. 72 °C. $[\alpha]_D^{23}$ = 47.9 (*c* = 4.70, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 5.20 (br. t, ^3J = 5.5 Hz, 1 H), 5.14 (dd, ^3J = 10.0, ^3J = 3.5 Hz, 1 H), 3.42 (ddd, ^2J = 12.0, ^3J = 6.5, ^3J = 5.5 Hz, 1 H), 3.26 (ddd, ^2J = 12.0, ^3J = 6.0, ^3J = 5.5 Hz, 1 H), 2.76 (m, 1 H), 1.84−1.65 (m, 3 H), 1.45 (s, 9 H), 1.23 (d, ^3J = 7.0 Hz, 3 H), 0.99 (d, ^3J = 6.5 Hz, 3 H), 0.96 (d, ^3J = 6.4 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 175.8, 175.2, 156.5, 79.9, 70.9, 43.5, 40.9, 39.9, 28.8, 25.1, 23.4, 21.9, 15.0 ppm. IR (film): $\tilde{\nu}$ = 3334 (br. s), 2962 (s), 1739 (s), 1727 (s), 1521 (s), 1458 (m), 1369 (m), 1253 (m), 1173 (s) cm^{-1}. HRMS (FAB): *m/z* calcd. $C_{15}H_{31}N_2O_6$ [M + NH_4^+] 335.2182, found 335.2212. LRMS (FAB): *m/z* (%) = 318.3 (21) [M + H^+], 279.2 (100), 263.2 (61), 218.2 (58), 104.1 (16).

(2*S*)-2-[(3′-{[(*tert*-Butoxy)carbonyl]amino}propionyl)oxy]-4-methylpentanoic Acid (33): A solution of **27** (1.05 g, 5.11 mmol), **31**[46] (966 mg, 5.11 mmol), DCC (1.05 g, 5.11 mmol) and DMAP (312 mg, 2.55 mmol) in DCM (50 mL) was stirred at room temperature for 12 h. The reaction was quenched with saturated aqueous NH_4Cl and the organic layer was dried with Na_2SO_4. Evaporation of the solvent and chromatographic purification (30% EtOAc in hexane) afforded (2*S*,2′*R*)-benzyl 2-[(3′-{[(*tert*-butoxy)carbonyl]-amino}propionyl)oxy]-4-methylpentanoate (1.83 g, 91%) as white solid. M.p. 63 °C. $[\alpha]_D^{23}$ = −27.8 (*c* = 0.94, $CHCl_3$) {ref.[33] $[\alpha]_D^{23}$ = −28.1 (*c* = 1.34, $CHCl_3$)}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.38 (m, 5 H), 5.23 (ABq, 2 H, *J* = 12.0 Hz, Δν = 12.0 Hz), 5.18 (br. s, 1 H), 5.13 (dd, ^3J = 9.5, ^3J = 4.0 Hz, 1 H), 3.44 (br. m, 2 H), 2.62 (t, ^3J = 6.0 Hz, 2 H), 1.84−1.70 (m, 2 H), 1.67 (m, 1 H), 1.47 (s, 9 H), 0.97 (d, ^3J = 5.5 Hz, 3 H), 0.93 (d, ^3J = 6.5 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 176.1, 171.0, 156.4, 135.6, 129.0, 128.9, 128.6, 79.8, 71.6, 67.5, 40.0, 36.7, 35.0, 28.8, 25.0, 23.4, 22.0 ppm. IR (film): $\tilde{\nu}$ = 3399 (br. m), 2962 (s), 2873 (w), 1743 (s), 1716 (s), 1509 (m), 1367 (m), 1250 (s), 1170 (s), 1078 (m), 749 (m) cm^{-1}. HRMS (CI): *m/z* calcd. $C_{21}H_{32}NO_6$ [M + H^+] 394.2230, found 394.2219. A mixture of (2*S*,2′*R*)-benzyl 2-[(3′-{[(*tert*-butoxy)carbonyl]amino}propionyl)oxy]-4-methylpentanoate (1.50 g, 3.81 mmol), 10% Pd/C (50 mg) and EtOAc (50 mL) was stirred for 1 h under H_2 and then filtered through a pad of Celite©. Concentration of the filtrate in vacuo yielded **33** (1.05 mg, 97%) as a white solid. M.p. 58 °C. $[\alpha]_D^{23}$ = −18.3 (*c* = 1.55, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 5.20 (br. s, 1 H), 5.13 (dd, ^3J = 9.0, ^3J = 4.5 Hz, 1 H), 3.47 (br. m, 2 H), 2.64 (br. m, 2 H), 1.85−1.75 (m, 2 H), 1.73 (m, 1 H), 1.46 (s, 9 H), 0.99 (d, ^3J = 6.0 Hz, 3 H), 0.96 (d, ^3J = 6.5 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 175.6, 172.5, 156.4, 80.0, 71.2, 39.9, 36.7, 35.0, 28.5, 25.1, 23.4, 21.9 ppm. IR (film): $\tilde{\nu}$ = 2961 (w), 2874 (w), 1741 (s), 1722 (s), 1521 (m), 1368 (s), 1251 (s), 1170 (s), 1076 (m) cm^{-1}. HRMS (CI): *m/z* calcd. $C_{14}H_{25}NNaO_6$ [M + Na^+] 326.1580, found 326.1589.

(2*S*,2′*R*,1′′*S*,2′′*R*,1′′′′*R*)-1′′-(3′′′-{1′′′′-[(*tert*-Butoxy)carbonyl]-2′′′′-*p*-methoxyphenylethylcarbamoyl}allyl)-2′′-methyl-4′′-phenylbut-3′′-enyl 2-[(3′-{[(*tert*-Butoxy)carbonyl]amino}-2′-methylpropionyl)oxy]-4-methylpentanoate (34): To a solution of **32** (794 mg, 2.50 mmol) in THF (10 mL) were successively added *i*Pr_2NEt (436 mL, 2.50 mmol) and 2,4,6-trichlorobenzyl chloride (391 mL, 2.50 mmol). After 2 h of stirring at room temperature, the solvent was evaporated and the residue was dissolved in benzene (20 mL). **25** (400 mg, 0.83 mmol) and DMAP (306 mg, 2.50 mmol) were added and the mixture was stirred at room temperature for a further 1 h. The reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with diethyl ether. The organic layer was dried with Na_2SO_4, concentrated in vacuo and chromatographically purified (30% EtOAc in hexane) to yield **34** (549 mg, 84%) as a white solid. M.p. 184 °C. $[\alpha]_D^{23}$ = −26.9 (*c* = 0.26, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.37−7.30 (m, 4 H), 7.25 (dd, ^3J = 8.0, ^3J = 7.7 Hz, 1 H), 7.09 (d, ^3J = 8.5 Hz, 2 H), 6.83 (m, 3 H), 6.43 (d, ^3J = 16.0 Hz, 1 H), 6.32 (d, ^3J = 6.0 Hz, 1 H), 6.04 (dd, ^3J = 16.0, ^3J = 8.5 Hz, 1 H), 5.91 (d, ^3J = 16.0 Hz, 1 H), 5.25 (t, ^3J = 4.5 Hz, 1 H), 5.06 (dd, ^3J = 5.5, ^3J = 4.5 Hz, 1 H), 4.96 (dd, ^3J = 10.0, ^3J = 5.0 Hz, 1 H), 4.82 (ddd, 1 H, ^3J = 7.5, ^3J = 4.0, ^3J = 1.6 Hz), 3.79 (s, 3 H), 3.47 (m, 2 H), 3.09 (d, ^3J = 6.5 Hz, 1 H), 2.77 (m, 1 H), 2.64 (m, 1 H), 2.56 (m, 2 H), 1.75−1.68 (m, 2 H), 1.58 (m, 1 H), 1.46 (s, 9 H), 1.43 (s, 9 H), 1.22 (d, ^3J = 6.0 Hz, 3 H), 1.13 (d, ^3J = 6.5 Hz, 3 H), 0.88 (d, ^3J = 6.5 Hz, 3 H), 0.85 (d, ^3J = 6.5 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 175.4, 171.2, 170.8, 165.2, 158.9, 156.5, 138.9, 137.3, 132.1, 131.0, 130.6, 129.0, 128.7, 127.8, 126.6, 126.5, 114.1, 82.6, 79.5, 76.9, 71.6, 55.6, 54.2, 43.4, 41.4, 40.4, 39.9, 37.7, 33.9, 28.8, 28.4, 25.0, 23.3, 21.8, 17.1, 15.0 ppm. IR (film): $\tilde{\nu}$ = 3400 (br. s), 2964 (s), 2934 (s), 1737 (s), 1678 (m), 1641 (m), 1513 (s), 1367 (s), 1249 (s), 1175 (s) cm^{-1}. HRMS (FAB): *m/z* calcd. $C_{44}H_{63}N_2O_{10}$ [M + H^+] 779.4483, found 779.4480.

(2*S*,1′′*S*,2′′*R*,1′′′′*R*)-1′′-[3′′′-({1′′′′-[(*tert*-Butoxy)carbonyl]-2′′′′-(*p*-methoxyphenyl)ethyl}carbamoyl)allyl]-2′′-methyl-4′′-phenylbut-3′′-enyl 2-[(3′-{[(*tert*-Butoxy)carbonyl]amino}propionyl)oxy]-4-methylpentanoate (35): To a solution of **33** (38.0 mg, 125 μmol) in THF (3 mL) were successively added *i*Pr_2NEt (22 μL, 125 μmol) and 2,4,6-trichlorobenzyl chloride (20 μL, 125 μmol). After 2 h of stirring at room temperature, the solvent was evaporated and the residue was dissolved in benzene (6 mL). **25** (30.0 mg, 62.6 μmol) and DMAP (15.0 mg, 125 μmol) were added and the mixture was stirred at room temperature for a further 1 h. The reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with diethyl ether. The organic layer was dried with Na_2SO_4, concentrated in vacuo and chromatographically purified (35% EtOAc in hexane) to yield **35** (38.0 mg, 80%) as a white solid. M.p. 175 °C. $[\alpha]_D^{23}$ = +7.9 (*c* = 0.38, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.37−7.30 (m, 4 H), 7.24 (dd, ^3J = 7.8, ^3J = 7.8 Hz, 1 H), 7.09 (d, ^3J = 8.5 Hz, 2 H), 6.82 (m, 3 H), 6.43 (d, ^3J = 16.0 Hz, 1 H), 6.38 (d, ^3J = 6.4 Hz, 1 H), 6.04 (dd, ^3J = 16.0, ^3J = 8.5 Hz, 1 H), 5.91 (d, ^3J = 16.0 Hz, 1 H), 5.29 (br. s, 1 H), 5.06 (dd, ^3J = 5.5, ^3J = 4.5 Hz, 1 H), 4.94 (dd, ^3J = 10.0, ^3J = 4.0 Hz, 1 H), 4.82 (ddd, 1 H, ^3J = 5.6, ^3J = 4.0, ^3J = 1.6 Hz), 3.78 (s, 3 H), 3.47 (m, 2 H), 3.08 (d, ^3J = 6.0 Hz, 1 H), 2.70−2.51 (m, 5 H), 1.76−1.68 (m, 2 H), 1.58 (m, 1 H), 1.45 (s, 9 H), 1.43 (s, 9 H), 1.13 (d, ^3J = 6.5 Hz, 3 H), 0.88 (d, ^3J = 6.5 Hz, 3 H), 0.86 (d, ^3J = 6.5 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 172.7, 171.3, 170.8, 165.3, 159.0, 156.4, 139.0, 137.3, 132.1, 131.0, 130.6, 129.0, 128.7, 127.9, 126.6, 114.1, 82.6, 79.8, 76.9, 71.2, 55.6, 54.1, 41.4, 40.0, 37.7, 36.5, 34.9, 34.0, 28.8, 28.4, 25.0, 23.3, 21.8, 17.2 ppm. IR (film): $\tilde{\nu}$ = 3340 (br. s), 2964 (s), 2932 (s), 1739 (s), 1677 (m), 1641 (m), 1513 (s), 1367 (s), 1249 (s), 1167 (s) cm^{-1}. HRMS (FAB): *m/z* calcd. $C_{43}H_{61}N_2O_{10}$ [M + H^+] 765.4326, found 765.4341.

Cryptophycin D (4): A mixture of **34** (288 mg, 0.37 mmol) and TFA (20 mL) was stirred at room temperature for 2 h. The reaction mixture was concentrated in vacuo and the residue was dissolved in THF (50 mL). To this solution were successively added *i*Pr_2NEt

(225 μL, 1.29 mmol), 2,4,6-trichlorobenzyl chloride (58 μL, 0.37 mmol) and DMAP (90 mg, 0.37 mmol). After stirring at room temperature for 1 h, the solvent was evaporated and the residue was dissolved in benzene (20 mL) and stirred at room temperature for 12 h. The reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with diethyl ether. The organic layer was dried with Na_2SO_4, concentrated in vacuo and chromatographically purified (50% EtOAc in hexane) to yield **4** (169 mg, 76%) as a white solid. M.p. 186−189 °C. $[\alpha]_D^{23}$ = +36.2 (*c* = 0.72, MeOH) {ref.[2] $[\alpha]_D^{23}$ = +36.7 (*c* = 1.93, MeOH)}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.36−7.31 (m, 4 H), 7.26 (dd, ^3J = 7.0, ^3J = 7.0 Hz, 1 H), 7.13 (d, ^3J = 8.5 Hz, 2 H), 7.08 (dd, ^3J = 6.0, ^3J = 6.0 Hz, 1 H), 6.83 (d, ^3J = 8.5 Hz, 2 H), 6.73 (ddd, ^3J = 15.0, ^3J = 10.0, ^3J = 5.0 Hz, 1 H), 6.42 (d, ^3J = 15.5 Hz, 1 H), 6.03 (dd, ^3J = 15.5, ^3J = 9.0 Hz, 1 H), 5.77 (d, ^3J = 15.0 Hz, 1 H), 5.67 (d, ^3J = 8.0 Hz, 1 H), 5.05 (ddd, 1 H, ^3J = 8.5, ^3J = 6.0, ^3J = 1.0 Hz), 4.87 (dd, ^3J = 10.0, ^3J = 3.0 Hz, 1 H), 4.81 (dt, ^3J = 7.5, ^3J = 7.5 Hz, 1 H), 3.80 (s, 3 H), 3.42 (dd, ^3J = 5.0, ^3J = 5.0 Hz, 2 H), 3.16 (dd, ^2J = 14.0, ^3J = 5.0 Hz, 1 H), 3.10 (dd, ^2J = 14.0, ^3J = 7.5 Hz, 1 H), 2.70 (m, 1 H), 2.56 (m, 2 H), 2.40 (m, 1 H), 1.68 (m, 2 H), 1.36 (m, 1 H), 1.25 (d, ^3J = 7.5 Hz, 3 H), 1.15 (d, ^3J = 7.0 Hz, 3 H), 0.78 (d, ^3J = 6.5 Hz, 3 H), 0.74 (d, ^3J = 6.5 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 176.4, 171.6, 171.2, 165.7, 159.0, 141.9, 137.1, 132.2, 130.6, 130.5, 129.0, 128.9, 128.0, 126.6, 125.5, 114.5, 77.6, 72.0, 55.6, 54.3, 42.7, 41.2, 40.1, 38.5, 36.9, 35.8, 24.9, 23.1, 21.6, 17.8, 14.6 ppm. IR (CH_2Cl_2): $\tilde{\nu}$ = 3420 (m), 2963 (s), 2936 (m), 1746 (s), 1721 (s), 1680 (s), 1649 (s), 1513 (s), 1248 (s), 1179 (s) cm^{-1}. HRMS (FAB): *m*/*z* calcd. $C_{35}H_{45}N_2O_7$ [M + H$^+$] 605.3227, found 605.3231.

Deoxyarenastatin A (36): A mixture of **35** (56.9 mg, 74.4 μmol) and TFA (10 mL) was stirred at room temperature for 2 h. The reaction was concentrated in vacuo and the residue was dissolved in THF (10 mL). To this solution were successively added *i*Pr$_2$NEt (12 μL, 74.4 μmol), 2,4,6-trichlorobenzyl chloride (12 μL, 74.4 μmol) and DMAP (36.0 mg, 298 μmol). After 1 h of stirring at room temperature, the solvent was evaporated and the residue was dissolved in benzene (10 mL) and stirred at room temperature for 1 h. The reaction was quenched with saturated aqueous NH_4Cl and the mixture extracted with diethyl ether. The organic layer was dried with Na_2SO_4, concentrated in vacuo and chromatographically purified (65% EtOAc in hexane) to yield **36** (35.2 mg, 81%) as a white solid. M.p. 182−188 °C. $[\alpha]_D^{23}$ = +33.5 (*c* = 0.09, CH_2Cl_2) {ref.[2] $[\alpha]_D^{23}$ = +34.0 (*c* = 1.36, CH_2Cl_2)}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.36−7.26 (m, 4 H), 7.23 (dd, ^3J = 7.8, ^3J = 7.8 Hz, 1 H), 7.12 (d, ^3J = 8.8 Hz, 2 H), 7.02 (dd, ^3J = 4.5, ^3J = 4.5 Hz, 1 H), 6.82 (d, ^3J = 8.8 Hz, 2 H), 6.71 (ddd, ^3J = 15.2, ^3J = 10.4, ^3J = 4.8 Hz, 1 H), 6.40 (d, ^3J = 15.6 Hz, 1 H), 6.01 (dd, ^3J = 15.6, ^3J = 8.5 Hz, 1 H), 5.73 (d, ^3J = 15.2 Hz, 1 H), 5.59 (d, ^3J = 8.0 Hz, 1 H), 5.05 (ddd, 1 H, ^3J = 9.6, ^3J = 6.8, ^3J = 1.3 Hz), 4.90 (dd, ^3J = 9.6, ^3J = 3.6 Hz, 1 H), 4.74 (dd, ^3J = 7.2, ^3J = 6.4 Hz, 1 H), 3.78 (s, 3 H), 3.55 (m, 1 H), 3.42 (m, 1 H), 3.14 (dd, ^2J = 14.4, ^3J = 6.0 Hz, 1 H), 3.05 (dd, ^2J = 14.4, ^3J = 7.6 Hz, 1 H), 2.54 (m, 4 H), 2.36 (dt, ^2J = 14.0, ^3J = 11.2 Hz, 1 H), 1.68 (m, 2 H), 1.40 (m, 1 H), 1.14 (d, ^3J = 6.8 Hz, 3 H), 0.74 (d, ^3J = 6.0 Hz, 3 H), 0.71 (d, ^3J = 6.0 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 173.3, 171.2, 171.1, 165.9, 159.0, 141.9, 137.1, 132.2, 130.6, 130.5, 129.0, 128.9, 128.0, 126.6, 125.5, 114.5, 77.0, 72.0, 55.6, 54.5, 42.7, 40.1, 36.8, 35.6, 34.6, 32.9, 24.8, 23.0, 21.7, 17.7 ppm. IR (film): $\tilde{\nu}$ = 2957 (s), 2925 (s), 1741 (s), 1730 (s), 1678 (s), 1650 (s), 1513 (s), 1372 (m), 1247 (s), 1175 (s) cm^{-1}. HRMS (FAB): *m*/*z* calcd. $C_{34}H_{43}N_2O_7$ [M + H$^+$] 591.3070, found 591.3080. LRMS (LCQ): *m*/*z* (%) = 591.1 (22) [M + H$^+$], 387.9 (100), 360.0 (35).

Cryptophycin B (2): To a solution of **4** (6.0 mg, 9.92 μmol) in DCM (2 mL) was added dimethyldioxirane[47] (0.32 M in acetone, 310 μL, 99.2 μmol) at −30 °C. The resulting mixture was stirred at −30 °C to room temperature for 12 h and then concentrated in vacuo. Chromatographic purification [HPLC, YMC-PACK OD-AQ 5S 120Å 4.6 × 250 mm, MeOH/H_2O, 3:1, 1 mL/min, room temp., t_R(**2**) = 31.58 min] to yield **2** (5.4 mg, 87%, 3:1) as a white solid. $[\alpha]_D^{23}$ = +20.6° (*c* = 0.24, MeOH) {ref.[2] $[\alpha]_D^{23}$ = +20.4 (*c* = 0.54, MeOH)}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.42−7.35 (m, 3 H), 7.28−7.24 (m, 2 H), 7.12 (d, ^3J = 8.5 Hz, 2 H), 7.06 (dd, ^3J = 5.9, ^3J = 5.9 Hz, 1 H), 6.84 (d, ^3J = 8.5 Hz, 2 H), 6.73 (ddd, ^3J = 15.1, ^3J = 10.1, ^3J = 4.8 Hz, 1 H), 5.73 (d, ^3J = 15.4 Hz, 1 H), 5.66 (d, ^3J = 8.2 Hz, 1 H), 5.21 (ddd, 1 H, ^3J = 9.5, ^3J = 4.8, ^3J = 1.6 Hz), 4.84 (dd, ^3J = 9.8, ^3J = 3.3 Hz, 1 H), 4.81 (dt, ^3J = 7.2, ^3J = 6.4 Hz, 1 H), 3.81 (s, 3 H), 3.71 (d, ^3J = 1.7 Hz, 1 H), 3.44 (ddd, ^2J = 13.6, ^3J = 12.7, ^3J = 5.5 Hz, 1 H), 3.39 (ddd, ^2J = 13.6, ^3J = 4.2, ^3J = 4.1 Hz, 1 H), 3.15 (dd, ^2J = 14.6, ^3J = 5.6 Hz, 1 H), 3.10 (dd, ^2J = 14.4, ^3J = 6.9 Hz, 1 H), 2.94 (dd, ^3J = 7.6, ^3J = 1.8 Hz, 1 H), 2.71 (m, 1 H), 2.58 (dm, 1 H, ^2J = 14.5 Hz), 2.40 (ddd, 1 H, ^2J = 14.5, ^3J = 10.8, ^3J = 10.5 Hz), 1.81 (m, 1 H), 1.73 (m, 2 H), 1.36 (m, 1 H), 1.25 (d, ^3J = 7.3 Hz, 3 H), 1.17 (d, ^3J = 6.9 Hz, 3 H), 0.88 (d, ^3J = 6.5 Hz, 3 H), 0.86 (d, ^3J = 6.5 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 176.4, 171.5, 171.1, 165.5, 159.0, 141.6, 137.1, 130.6, 129.1, 129.0, 128.7, 126.0, 125.5, 114.6, 76.7, 71.7, 63.5, 59.5, 55.6, 54.3, 41.2, 39.8, 38.5, 37.2, 35.7, 24.9, 23.3, 21.7, 14.7, 14.0 ppm. IR (DCM): $\tilde{\nu}$ = 3411 (m), 2962 (s), 2935 (m), 1743 (s), 1724 (s), 1682 (s), 1513 (s), 1247 (s), 1199 (s), 1179 (s) cm^{-1}. HRMS (FAB): *m*/*z* calcd. $C_{35}H_{45}N_2O_8$ [M + H$^+$] 621.3176, found 621.3160.

Arenastatin A (5): To a solution of **36** (5.2 mg, 8.81 μmol) in DCM (2 mL) was added dimethyldioxirane[45] (0.23 M in acetone, 383 μL, 88.1 μmol) at −30 °C. The resulting mixture was stirred at −30 °C to room temperature for 12 h and then concentrated in vacuo. Chromatographic purification [HPLC, YMC-PACK OD-AQ 5S 120Å 4.6 × 250 mm, MeOH/H_2O 3:1, 1 mL/min, room temp., t_R(**5**) = 30.86 min] to yield **5** (4.0 mg, 75%, 3:1) as a colorless film. $[\alpha]_D^{23}$ = +48.1 (*c* = 0.09, $CHCl_3$) {ref.[33] $[\alpha]_D^{23}$ = +48.7 (*c* = 0.87, $CHCl_3$)[. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.43−7.24 (m, 5 H), 7.11 (d, ^3J = 8.5 Hz, 2 H), 7.04 (t, ^3J = 5.9 Hz, 1 H), 6.83 (d, ^3J = 8.6 Hz, 2 H), 6.72 (ddd, ^3J = 15.1, ^3J = 10.2, ^3J = 4.8 Hz, 1 H), 5.72 (d, ^3J = 15.2 Hz, 1 H), 5.65 (d, ^3J = 8.2 Hz, 1 H), 5.21 (ddd, 1 H, ^3J = 9.4, ^3J = 4.8, ^3J = 1.5 Hz), 4.90 (dd, ^3J = 9.8, ^3J = 3.4 Hz, 1 H), 4.75 (dt, ^3J = 7.3, ^3J = 6.3 Hz, 1 H), 3.78 (s, 3 H), 3.71 (d, ^3J = 1.8 Hz, 1 H), 3.46 (ddd, ^2J = 13.4, ^3J = 12.6, ^3J = 5.5 Hz, 1 H), 3.41 (ddd, ^2J = 13.5, ^3J = 4.2, ^3J = 4.2 Hz, 1 H), 3.15 (dd, ^2J = 14.6, ^3J = 5.3 Hz, 1 H), 3.08 (dd, ^2J = 14.5, ^3J = 6.7 Hz, 1 H), 2.94 (dd, ^3J = 7.6, ^3J = 1.8 Hz, 1 H), 2.58 (m, 3 H), 2.39 (ddd, 1 H, ^3J = 7.6, ^3J = 7.5, ^3J = 7.5 Hz), 1.75−1.69 (m, 3 H), 1.32 (m, 1 H), 1.15 (d, ^3J = 6.9 Hz, 3 H), 0.84 (d, ^3J = 6.5 Hz, 3 H), 0.83 (d, ^3J = 6.5 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 173.2, 171.1, 171.0, 165.8, 159.0, 141.5, 137.1, 130.6, 129.1, 128.9, 128.7, 126.0, 125.5, 114.5, 77.5, 71.7, 63.5, 59.5, 55.6, 54.5, 42.7, 40.1, 36.9, 35.6, 34.6, 32.9, 24.8, 23.1, 21.7, 14.0 ppm. IR (film): $\tilde{\nu}$ = 3410 (m), 2963 (s), 2932 (m), 1742 (s), 1726 (s), 1679 (s), 1513 (s), 1246 (s), 1200 (m), 1180 (s) cm^{-1}. HRMS (FAB): *m*/*z* calcd. $C_{34}H_{43}N_2O_8$ [M + H$^+$] 607.3019, found 607.3025.

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