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Synthesis of Cryptophycins via an *N*-Acyl-*β*-lactam Macrolactonization

Ramdas Vidya,[†] MariJean Eggen,[†] Sajiv K. Nair,[†] Gunda I. Georg,*[,†] and Richard H. Himes[‡]

Department of Medicinal Chemistry and Department of Molecular Biosciences, University of Kansas, Lawrence, Kansas 66045

georg@ku.edu

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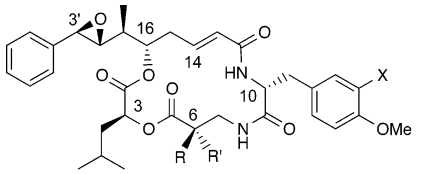
An efficient and concise approach to the synthesis of the macrolide core of the cryptophycins has been developed. A novel macrolactonization utilizing a reactive acyl-*β*-lactam intermediate incorporates the *β*-amino acid moiety within the 16-membered macrolide core. This modular approach, involving a cyanide-initiated acyl-*β*-lactam ring opening followed by cyclization, was successfully applied to the total synthesis of cryptophycin-24. The strategy was also used in an efficient synthesis of the 6,6-dimethyl-substituted dechlorocryptophycin-52. In this case, the cyanide-initiated ring opening of the bis-substituted 2-azetidinone followed by macrolactonization was achieved through a catalytic process.

Cryptophycins are potent, tumor-selective tubulin-binding antimitotic agents[1] with excellent activity against multidrug-resistant (MDR) cancer cells.[2−7] Cryptophycin-1 (**1**, Figure 1), initially isolated from the blue green algae *Nostoc* sp. ATCC 53789[8] and later from GSV 224,[9,10] is the major cytotoxic metabolite. Cryptophycin-1 is an effective inhibitor of tubulin polymerization at substoichiometric concentrations,[11] and inhibits vinblastine binding to tubulin.[11−15] Additional studies with tubulin suggest that upon binding cryptophycin-1 induces the formation of ring structures, possibly resulting from curvature at two points per heterodimer, with local changes in the *β*-subunit and long-range changes affecting the α-subunit.[16,17] A structurally related compound, arenastatin A, also called cryptophycin-24 (**2**, Figure 1), was isolated from the Okinawan marine sponge *Dysidea arenaria*[18,19] and from *Nostoc* sp. GSV 224.[20] It is a potent inhibitor of tubulin polymerization[21] and possesses excellent cytotoxicity against KB cells in vitro.[18,19] In addition to their action against tubulin and microtubules, the



R	R'	X	
Me	H	Cl	Cryptophycin-1 (**1**)
H	H	H	Cryptophycin-24 (Arenastatin A) (**2**)
Me	Me	Cl	Cryptophycin-52 (**3**)
Me	Me	H	Dechlorocryptophycin-52 (**4**)

FIGURE 1. Structures of cryptophycins.

[†] Department of Medicinal Chemistry.
[‡] Department of Molecular Biosciences.

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cryptophycins also inhibit DNA and RNA synthesis[22] and induce apoptosis.[23,24] Cryptophycin-induced apoptosis is accompanied by phosphorylation of c-raf1, bcl-2, bcl-x_L, and c-Jun NH_2-terminal kinase.[23] Cryptophycin-24 is completely devoid of activity in vivo as it has a half-life of only 10 min in mouse serum[25] due to rapid hydrolysis of the C5 ester.

Cryptophycin-52 (**3**, Figure 1), a synthetic analogue[2,3] that carries a *gem*-dimethyl group at the C6 position, displays increased hydrolytic stability and improved in vivo antitumor efficacy compared to cryptophycin-1.[3] Cryptophycin-52 displays high cytotoxicity against numerous cancer cell lines, including MDR cancer cell lines, and is the most potent suppressor of microtubule dynamics found to date.[26,27] Because of these attributes, cryptophycin-52 (**3**) was selected for clinical development[3] and has been under evaluation.[28] Recently, a patent has described cryptophycin-308, the glycine ester of the chlorohydrin of cryptophycin-1 (**1**, Figure 1), as possessing better aqueous solubility, superior microtubule disruption, and lower toxicities than derivatives previously disclosed.[29]

The potent bioactivity of the cryptophycins attracted several research groups, including ours, leading to a large number of reported formal[30−35] and total syntheses.[2,36−45] Significant structure−activity relationship studies have also been carried out involving both semisynthetic analogues derived from modifications of the epoxide[20,46] and synthetic analogues which differ in the tyrosine fragment,[47] β-amino acid moiety,[48] or octadienoate ester fragment[49] or contain an isosteric replacement of the C5 ester with an amide.[50]

Our previous experience with the use of chiral β-lactam precursors prompted us to examine the idea of deriving the β-amino acid within the cryptophycin core from such a synthon. *N*-Acyl-β-lactams were shown to be excellent sources for the incorporation of the phenylisoserine side chain of paclitaxel, and readily reacted with the alkoxide of baccatin III.[51] A similar approach involving the intramolecular reaction[52−54] of the β-hydroxy group of the leucic acid ester with the activated acyl β-lactam intermediate (**5a**, **5b**) could represent a novel, concise approach toward the synthesis of the macrolide core of the cryptophycins and did provide the basis for our retrosynthetic strategy (Figure 2).

The retrosynthetic analysis for cryptophycins reveals that the molecule can be assembled from three basic building blocks, octadienoate esters **6**, L-leucic acid derivative **7**, and *N*-acylazetidinones **8** (Figure 2). The introduction of the 3′-phenyl group of the cryptophycins can be accomplished by a Heck reaction, either at an early stage in the synthesis by attaching the phenyl group to octadienoate **6a**, or later in the synthetic scheme. This approach makes the synthesis flexible for incorporation of various aryl substituents at the C3′ position.

The synthesis of cryptophycin-24 (**2**) started with secondary alcohol **9**,[31] which was coupled with acid chloride **7**, derived from bis-silylated L-leucic acid,[55] to provide ester **10** in 75% yield (Scheme 1). Oxidation of the primary alcohol, obtained after deprotection of the *p*-methoxybenzyl group of **10**, was found to be problematic as basic oxidation conditions led to significant decomposition and byproduct formation. However, the Dess−Martin oxidation cleanly provided the required aldehyde in 81% yield. The next step in the synthesis, the Horner−Emmons homologation of the aldehyde, was also problematic under basic reaction conditions, including Masamune and Roush conditions (LiCl/DBU).[56] Neutral reaction conditions and the use of phosphorane **11** produced the desired ester **12** in 94% yield (Scheme 1).

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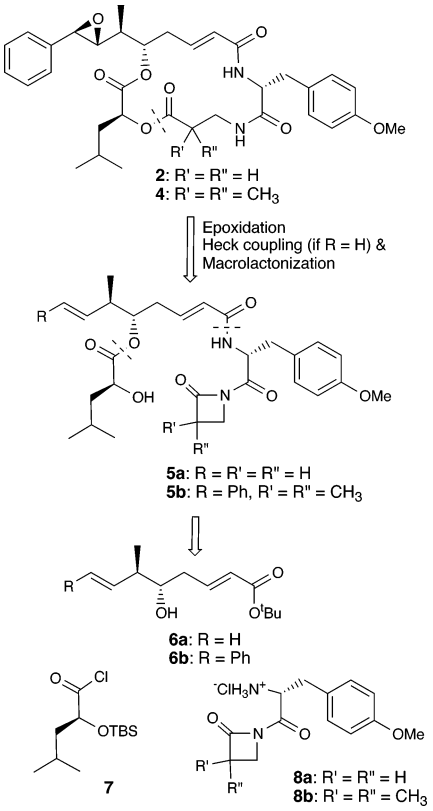
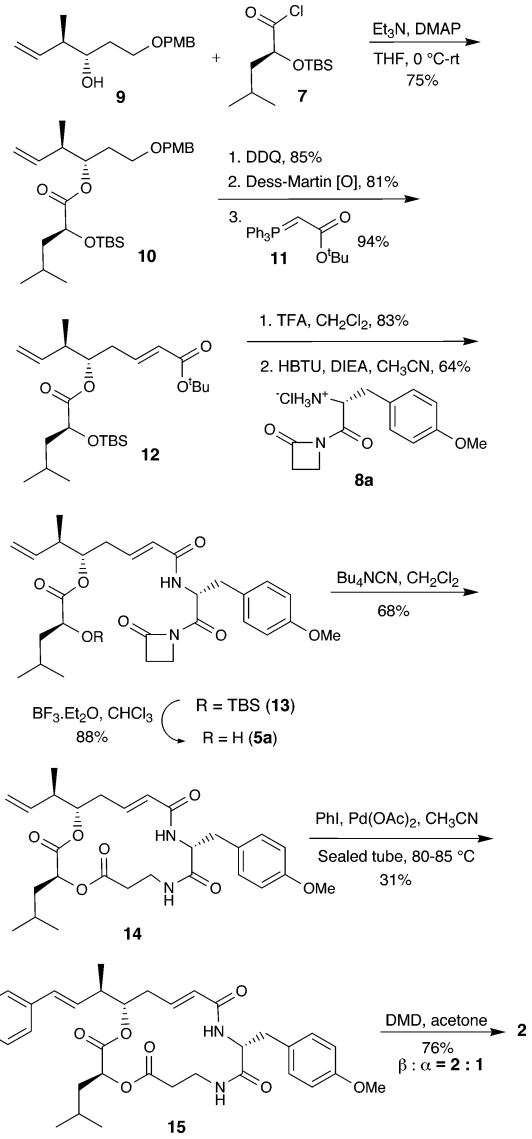


FIGURE 2. Retrosynthetic analysis.

Ester cleavage with TFA, followed by coupling with aminoacylazetidinone **8a** using HBTU/DIEA, provided acyl-β-lactam intermediate **5a** in 88% yield. Attempts to cyclize this intermediate with NaH and NaHMDS (paclitaxel conditions) were incompatible with this substrate, presumably as a result of its sensitivity to basic conditions. The reactions provided no isolable product and led to the formation of baseline material. The key macrolactonization was achieved with use of CH_2Cl_2-soluble Bu_4NCN[52] to furnish the 16-membered macrolide **14** in 68% yield (Scheme 1). Introduction of the C3′-phenyl group under Heck conditions produced the desepoxy analogue **15**[41] in only 31% yield. The final epoxidation utilizing dimethyldioxirane (DMD)[40,57] provided a diastereomeric mixture of cryptophycin-24 (**2**, β:α = 2:1) in 76% yield, which was separated by reverse-phase HPLC.[58]

As an extension of this methodology, we were interested in the synthesis of the macrolide core of cryptophycin-52, the C6 *gem*-dimethyl-substituted derivative, which is under clinical development. Cryptophycin-52 was first prepared by Barrow et al. utilizing an asymmetric Sharpless epoxidation as a key step.[36] Later, the synthesis was modified by the group at Eli Lilly to produce a synthesis that involved more than 30 discrete synthetic operations.[3,38,59] Herein we describe a concise total synthesis of dechlorocryptophycin-52 (**4**) using dimethyl-2-azetidinone as a building block.

SCHEME 1



Since the late-stage Heck coupling provided a poor yield, octadienoate ester **6b** was synthesized from 1,3-propanediol by using a nine-step sequence reported earlier from our laboratory (17% overall yield).[41] Fragment **6b** was coupled with acid chloride **7**[55] with use of triethylamine and DMAP to afford the diester **16** in 92% yield (Scheme 2). The TBS and *tert*-butyl ester groups in compound **16** were deprotected simultaneously with excess TFA to provide hydroxy acid **17** in 90% yield.

The key *N*-acylazetidinone **8b** was prepared as shown in Scheme 3. β-Lactam **19**, prepared from ethyl cyanoacetate in three steps in 42% overall yield,[60−62] was coupled with tyrosine derivative **18**[36] with use of HBTU and DIEA to furnish **20** in 91% yield. The Boc group of amine **20** was cleaved in quantitative yield with 4 M HCl in 1,4-dioxane to afford **8b**.

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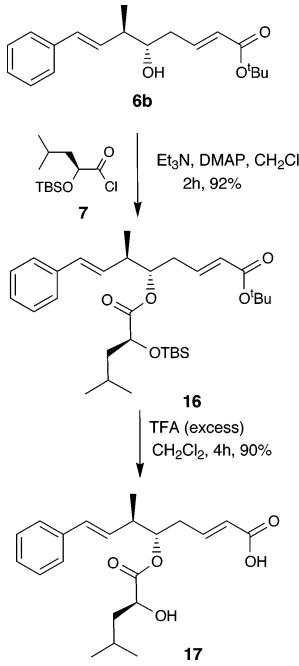
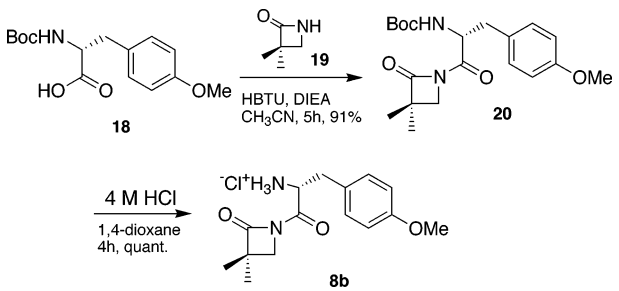
SCHEME 2

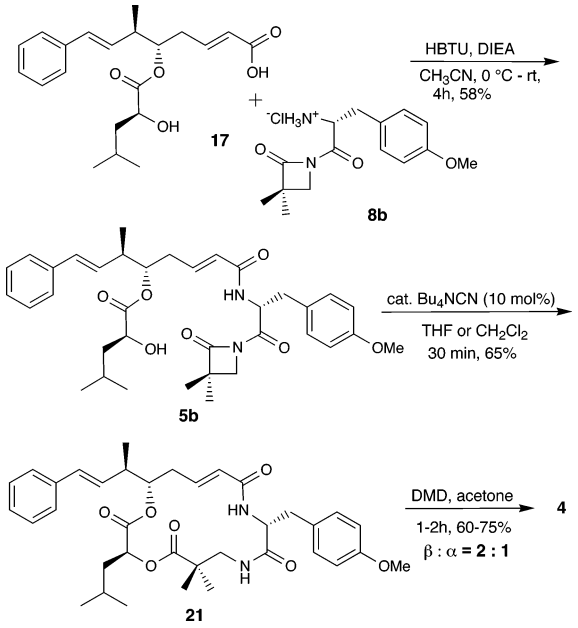


SCHEME 3



Coupling of hydroxy compound **17** and β-lactam **8b** with HBTU and DIEA furnished the macrolide precursor **5b**, which possessed all of the elements necessary for the formation of the macrocycle (Scheme 4). Initially, the simultaneous ring opening of the acyl-β-lactam followed by cyclization was tried with excess tetrabutylammonium cyanide as reported earlier.[42,52,63,64] Interestingly, we later found that the key macrolactonization can be achieved using a "catalytic" amount of tetrabutylammonium cyanide or potassium cyanide to produce the 16-membered macrolide **21** in 65% yield. The final epoxidation of **21** utilizing dimethyldioxirane (DMD)[57] provided a diastereomeric mixture of dechlorocryptophycin-52 (**4**) in a 2:1 (β:α) ratio and in 75% yield.[40,48] The mixture was separated by reverse-phase HPLC. The preliminary biological testing of the dechlorocryptophycin-52 analogue showed good activity in both the tubulin assembly assay [IC_{50} = 3 μM; for Cr-1, IC_{50} = 2.5 μM] and the cytotoxicity assay [MCF-7 cell line, IC_{50} = 0.3 nM; for Cr-1, IC_{50} = 0.007 nM].[65,66] The α-isomer was found to be less active in both

SCHEME 4



assays [IC_{50} = 32 μM in the tubulin assembly assay; IC_{50} = 1.7 nM in the MCF-7 cell line].

In summary, a novel macrolactonization approach utilizing a reactive acyl-β-lactam for the incorporation of the β-amino acid moiety has been developed for a unique and convergent synthesis of cryptophycin-24 (**2**). This approach also allowed an efficient and convergent synthesis of dechlorocryptophycin-52 (**4**). The modular approach allows for multiple alterations throughout the structure by modification of the amino acyl β-lactam, hydroxy acid, and C3′-aromatic group. The acyl-β-lactam macrolactonization strategy provides a concise and efficient entry into the macrocyclic core of this promising family of antitumor macrolides.

Experimental Section

(1*S*,2*R*)-1-{2-[(4-Methoxyphenyl)methoxy]ethyl}-2-methylbut-3-enyl-(2*S*)-4-methyl-2-(1,1,2,2-tetramethyl-1-silapropoxy)pentanoate (10). To bis-TBS protected L-leucic acid (6.5 g, 18 mmol) in CH_2Cl_2 (30 mL) was added 15 drops of DMF.[55] The solution was cooled to 0 °C and oxalyl chloride (3.2 mL, 36 mmol) was added dropwise with an addition funnel. Vigorous bubbling was observed, which gradually subsided. After addition was complete, the mixture was warmed to room temperature and stirred at room temperature for 4.5 h. The mixture was concentrated in vacuo and used in the next step. The crude acid chloride **7** was added dropwise to a solution of alcohol **9**[41] (1.5 g, 6 mmol), DMAP (2.2 g, 18 mmol), and TEA (1.7 mL, 12 mmol) in CH_2Cl_2 (15 mL) at 0 °C. The reaction was stirred at 0 °C for 45 min at which time TLC indicated the disappearance of alcohol **9**. The reaction was quenched with saturated aqueous $NaHCO_3$ and Et_2O. The aqueous layer was extracted with Et_2O. The combined organic layers were dried ($MgSO_4$) and concentrated. Flash chromatography (hexanes to 95:5 hexanes:EtOAc) provided ester **10** as an oil (2.22 g, 78%). $[\alpha]_D$ −42 (*c* 1.5, $CHCl_3$); IR (film) 2920, 2820, 1730, 1625 cm^{-1}; ^1H NMR δ 7.25−7.23 (d, J = 8 Hz, 2H), 6.87−6.85 (d, J = 8 Hz, 2H), 5.77−5.68 (m, 1H), 5.08−

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5.05 (m, 2H), 5.02−5.01 (d, 5 Hz, 1H), 4.43−4.40 (d, J = 11 Hz, 1H), 4.37−4.34 (d, J = 11 Hz, 1H), 4.20−4.17 (dd, J = 9, 4 Hz, 1H), 3.79 (s, 3H), 3.48−3.36 (m, 2H), 2.43−2.38 (m, 1H), 1.85−1.83 (d, J = 7 Hz, 1H), 1.82−1.80 (d, J = 7 Hz, 1H), 1.75 (m buried, 1H), 1.64−1.57 (ddd, J = 5, 9, 14 Hz, 1H), 1.50−1.44 (ddd, J = 4, 9, 14 Hz, 1H), 1.00−0.99 (d, J = 7 Hz, 3H), 0.92−0.91 (d, J = 7 Hz, 3H), 0.91 (buried, 3H), 0.90 (s, 9H), 0.07 (s, 3H), 0.04 (s, 3H); ^{13}C NMR δ 173.8, 159.1, 139.0, 130.4, 129.2 (2C), 115.8, 113.7 (2C), 74.3, 72.7, 70.7, 66.5, 55.2, 44.3, 41.6, 31.6, 25.7 (3C), 24.1, 23.4, 21.7, 18.2, 15.7, −4.6, −5.3; MS (EI) m/z 477 (M − 1).

Three-Step Synthesis of 12 from 10. 1. DDQ Deprotection of 10 To Form Intermediate Alcohol: 1-[(1*R*)-1-Methylprop-2-enyl]-(1*S*)-3-hydroxypropyl-(2*S*)-4-methyl-2-(1,1,2,2-tetramethyl-1-silapropoxy)pentanoate. Ester **10** (276 mg, 0.577 mmol) was dissolved in CH_2Cl_2 (2 mL) and H_2O (0.1 mL). The mixture was cooled to 0 °C and DDQ (144 mg, 0.635 mmol) was added. After 30 min at 0 °C, the bath was removed and the mixture was stirred an additional 90 min at room temperature. Additional CH_2Cl_2 was added and the organic layer was washed with saturated aqueous $NaHCO_3$ solution. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Flash chromatography (hexanes to 85:15 hexanes:EtOAc) provided the desired alcohol (176 mg, 85%) as an oil (often a mixture of alcohol and aldehyde byproduct were utilized in the next reaction). IR (film) 3420, 2920, 2890, 1730 cm^{-1}; ^{1}H NMR δ 5.76−5.68 (ddd, J = 8, 10, 18 Hz, 1H), 5.08−4.99 (m, 3H), 4.25−4.22 (dd, J = 4, 9 Hz, 1H), 3.65−3.60 (m, 1H), 3.51−3.45 (ddd, J = 4, 10, 11 Hz, 1H), 2.42−2.37 (m, 2H), 1.84−1.75 (m, 2H), 1.71−1.58 (m, 2H), 1.54−1.47 (ddd, J = 4, 9, 13 Hz, 1H), 1.03−1.01 (d, J = 7 Hz, 1H), 0.92−0.91 (d, J = 7 Hz, 3H), 0.92−0.90 (d, J = 7 Hz, 3H), 0.89 (s, 9H), 0.07 (s, 3H), 0.04 (s, 3H); ^{13}C NMR δ 175.2, 139.0, 116.1, 74.5, 70.7, 58.5, 44.4, 41.9, 34.7, 25.7 (3C), 24.2, 23.4, 21.7, 18.2, 16.2, −4.7, −5.3.

2. Oxidation of DDQ Deprotected Alcohol to Intermediate Aldehyde: 1-[(1*R*)-1-Methylprop-2-enyl]-(1*S*)-3-oxopropyl-(2*S*)-4-methyl-2-(1,1,2,2-tetramethyl-1-silapropoxy)-pentanoate. The alcohol (95 mg, 0.265 mmol) was dissolved in CH_2Cl_2 (2.7 mL) and Dess−Martin periodinane (169 mg, 0.397 mmol) was added. After 2 h, a 1:1 mixture of saturated aqueous $Na_2S_2O_3$ and NH_4Cl solutions was added. After 10 min of vigorous stirring, the mixture was diluted with CH_2Cl_2 and H_2O. The aqueous phase was extracted with CH_2Cl_2. The combined extracts were washed with saturated aqueous $NaHCO_3$ solution, dried ($MgSO_4$), filtered, and concentrated. The product was a colorless oil (76 mg, 81%). IR (film) 3750, 2940, 2910, 2840, 1740, 1715 cm^{-1}; ^{1}H NMR δ 9.70 (dd, J = 2.5, 1.4 Hz, 1H), 5.76−5.67 (ddd, J = 17, 10, 8 Hz, 1H), 5.39−5.34 (dt, J = 8, 5 Hz, 1H), 5.11−5.09 (m, 1H), 5.10−5.06 (m, 1H), 4.19−4.16 (dd, J = 4, 9 Hz, 1H), 2.68−2.62 (ddd, J = 17, 8, 2.5 Hz, 1H), 2.62−2.56 (ddd, J = 17, 5, 1.4 Hz, 1H), 2.53−2.48 (m, 1H), 1.80−1.74 (m, 1H), 1.63−1.56 (ddd, J = 14, 9, 5 Hz, 1H), 1.48−1.42 (ddd, J = 14, 9, 4 Hz, 1H), 1.04−1.03 (d, J = 7 Hz, 3H), 0.92−0.89 (buried, 6H), 0.89 (s, 9H), 0.07 (s, 3H), 0.03 (s, 3H); ^{13}C NMR δ 199.2, 173.7, 138.2, 116.9, 71.7, 70.7, 45.5, 44.2, 41.3, 25.7 (3C), 24.1, 23.4, 21.7, 18.2, 15.5, −4.7, −5.4; MS (EI) m/z 357 (M$^+$ + H), 316; HRMS (FAB, m/z) calcd for $C_{19}H_{37}O_4Si$ (M$^+$ + H) 357.2461, found 357.2463.

3. Wittig Reaction of Intermediate Aldehyde To Form 12. *tert*-Butyl-(2*E*)-5-[(2*S*)-4-methyl-2-(1,1,2,2-tetramethyl-1-silapropoxy)pentanoyloxy]-(5*S*,6*R*)-6-methylocta-2,7-dienoate (12). The aldehyde (80 mg, 0.22 mmol) was dissolved in CH_2Cl_2 (2.2 mL) and cooled to 0 °C. (*tert*-Butoxycarbonylmethylene)triphenylphosphorane **11** (101 mg, 0.27 mmol) was added. After 30 min at 0 °C and 90 min at room temperature, the reaction was concentrated and purified by flash chromatography (95:5 hexane:EtOAc) to provide **12** as a colorless oil (96 mg, 94%). $[\alpha]_D$ −25 (*c* 0.50, $CHCl_3$); IR (film) 3070, 2935, 2910, 2840, 1740, 1700, 1645 cm^{-1}; ^{1}H NMR δ 6.77−6.69 (dt, J = 7, 15 Hz, 1H), 5.79−5.75 (d, J = 15 Hz, 1H), 5.75−5.66 (m, 1H), 5.08 (br s, 1H), 5.07−5.03 (m, 1H), 4.99−4.95 (app q, J = 6 Hz, 1H), 4.19−4.16 (dd, J = 4, 9 Hz, 1H), 2.45−2.38 (m, 3H), 1.81−1.74 (m, 1H), 1.63−1.57 (ddd, J = 5, 9, 13 Hz, 1H), 1.48−1.42 (buried, 1H), 1.45 (s, 9H), 1.02−1.00 (d, J = 7 Hz, 3H), 0.92−0.89 (buried, 6H), 0.89 (s, 9H), 0.06 (s, 3H), 0.02 (s, 3H); ^{13}C NMR δ 173.8, 165.3, 142.3, 138.6, 125.9, 116.3, 80.2, 75.3, 70.7, 44.3, 41.2, 34.1, 28.1 (3C), 25.7 (3C), 24.1, 23.4, 21.7, 18.2, 16.0, −4.6, −5.4; MS (EI) m/z 399 (9), 341 (9), 267 (20), 201 (100), 189 (100); HRMS (FAB, m/z) calcd for $C_{25}H_{47}O_5Si$ (M$^+$ + H) 455.3193, found 455.3171.

Two-Step Synthesis of 13 from 12. 1. Deprotection of Ester 12 to Intermediate Acid: (2*E*)-5-[(2*S*)-4-Methyl-2-(1,1,2,2-tetramethyl-1-silapropoxy)pentanoyloxy]-(5*S*,6*R*)-6-methylocta-2,7-dienoic Acid. The *tert*-butyl ester **12** (40 mg, 0.088 mmol) was dissolved in CH_2Cl_2 (0.1 mL) and cooled to 0 °C. A TFA solution (1 M in CH_2Cl_2, 1.1 mL) was added via syringe. The ice bath was removed after 2 h and the reaction was continued with vigorous stirring. After 6 h, the reaction was found to be complete by TLC. Toluene (0.10 mL) was added and the reaction was concentrated under vacuum to provide the acid as a colorless oil (29 mg, 83%). IR (film) 3060, 3000, 2930, 1740, 1715 cm^{-1}; ^{1}H NMR δ 6.99−6.92 (dt, J = 8, 15 Hz, 1H), 5.88−5.84 (br d, J = 15 Hz, 1H), 5.74−5.65 (ddd, J = 8, 10, 17 Hz, 1H), 5.09−4.99 (m, 3H), 4.19−4.16 (dd, J = 4, 9 Hz, 1H), 2.49−2.38 (m, 3H), 1.79−1.74 (m, 1H), 1.63−1.56 (ddd, J = 4, 9, 13 Hz, 1H), 1.45−1.38 (ddd, J = 4, 9, 13 Hz, 1H), 1.02−1.00 (d, J = 7 Hz, 3H), 0.91−0.90 (d, J = 4 Hz, 3H), 0.89−0.88 (d, J = 4 Hz, 3H), 0.88 (s, 9H), 0.06 (s, 3H), 0.02 (s, 3H); ^{13}C NMR δ 173.8, 146.7, 138.5, 123.3, 116.5, 75.0, 70.7, 44.4, 41.3, 34.5, 25.7 (3C), 24.1, 23.4, 21.7, 18.2, 16.1, −4.7, −5.4; MS (EI) m/z 399 (M$^+$ + H); HRMS (FAB, m/z) calcd for $C_{21}H_{39}O_5Si$ (M$^+$ + H) 399.2576, found 399.2559.

2. Formation of Amide 13 from Acid and Salt 8a: (3*E*)-4-(*N*-{(1*R*)-2-(3,3-Dimethyl-2-oxoazetidinyl)-1-[(4-methoxyphenyl)methyl]-2-oxoethyl}carbamoyl)-1-((1*R*)-1-methylprop-2-enyl)-(1*S*)-but-3-enyl-(2*S*)-4-methyl-2-(1,1,2-trimethyl-1-silapropoxy)pentanoate (13). The *N*-Boc protected (D)-tyrosine derivative[36] (120 mg, 0.41 mmol) was dissolved in CH_3CN (4 mL) and cooled to 0 °C. 2-Azetidinone (50 mg, 0.69 mmol), DIEA (142 μL, 0.81 mmol), and HBTU (262 mg, 0.69 mmol) were added consecutively. After 20 min, the ice bath was removed and the mixture was stirred for 1 h. The reaction was quenched with saturated aqueous NH_4Cl solution and extracted with EtOAc. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Flash chromatography (80:20 to 50:50 hexanes:EtOAc) provided (2*R*)-(*tert*-butoxy)-*N*-((4-methoxyphenyl)methyl)-2-oxo-2-((2-oxoazetidinyl)ethyl)formamide as a cream colored solid (85 mg, 60%). Mp 107−109°; $[\alpha]_D$ −56 (*c* 1.0, $CHCl_3$); IR (film) 3390, 1790, 1705, 1690 cm^{-1}; ^{1}H NMR δ 7.12−7.10 (d, J = 9 Hz, 2H), 6.82−6.80 (d, J = 9 Hz, 2H), 5.05 (br s, 2H), 3.76 (s, 3H), 3.64−3.59 (m, 1H), 3.51−3.46 (m, 1H), 3.08−2.98 (m, 3H), 2.82−2.78 (m, 1H), 1.35 (s, 9H); ^{13}C NMR δ 170.7, 164.7, 159.4, 155.7, 130.8 (2C), 128.1, 114.3 (2C), 80.4, 56.2, 55.7, 37.5, 36.9, 36.4, 28.7 (3C); MS(FAB+, NBA) m/z 349 (M$^+$ + H), 121 (100); HRMS (FAB, m/z) calcd for $C_{18}H_{25}N_2O_5$ (M$^+$ + H) 349.1763, found 349.1782.

This compound (150 mg, 0.431 mmol) was dissolved in 4 N HCl in dioxane (4 mL) and stirred for 1.5 h. A precipitate formed and the reaction was concentrated to provide a light tan salt **8a**. The acid (40 mg, 0.10 mmol) and salt **8a** (40 mg, 0.140 mmol) were placed in a flask and CH_3CN (1 mL) was added. The solution was cooled to 0 °C and DIEA (52 μL, 0.30 mmol) was added. When the solution was clear, HBTU (57 mg, 0.15 mmol) was added and the reaction stirred for 30 min at 0 °C and room temperature for 90 min. Saturated $NaHCO_3$ solution and CH_2Cl_2 were added. The aqueous layer was further extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Flash chromatography (70:30 to 40:60 hexane/EtOAc) provided the product **13** as a viscous oil (40 mg, 64%). IR (film) 3280, 3060, 2920, 2900, 2825, 1770, 1730, 1690, 1660, 1620 cm^{-1}; ^{1}H NMR δ 7.10−7.07 (d, J = 9 Hz, 2H), 6.82−6.80 (d, J = 9 Hz, 2H),

6.75−6.68 (dt, J = 7, 15 Hz, 1H), 5.98−5.96 (br d, J = 7 Hz, 1H), 5.82−5.78 (d, J = 15 Hz, 1H), 5.73−5.65 (m, 1H), 5.39−5.34 (app q, J = 7 Hz, 1H), 5.06−5.01 (m, 2H), 4.94−4.89 (app q, J = 6 Hz, 1H), 4.18−4.15 (dd, J = 4, 9 Hz, 1H), 3.77 (s, 3H), 3.64−3.59 (m, 1H), 3.53−3.48 (m, 1H), 3.15−3.10 (dd, J = 6, 14 Hz, 1H), 3.08−2.99 (m, 2H), 2.97−2.91 (dd, J = 7, 14 Hz, 1H), 2.43−2.39 (m, J = 7 Hz, 3H), 1.80−1.73 (m, 1H), 1.62−1.55 (ddd, J = 5, 9, 13 Hz, 1H), 1.47−1.41 (ddd, J = 4, 9, 13 Hz, 1H), 0.99−0.98 (d, J = 7 Hz, 3H), 0.91−0.89 (d, J = 7 Hz, 3H), 0.90−0.88 (d, J = 7 Hz, 3H), 0.88 (s, 9H), 0.04 (s, 3H), 0.01 (s, 3H); ^{13}C NMR δ 173.8, 169.5, 164.7, 164.2, 158.8, 140.1, 138.6, 130.3 (2C), 127.2, 125.6, 116.3, 114.0 (2C), 75.4, 70.7, 55.2, 54.5, 44.3, 40.8, 36.7, 36.6, 36.0, 34.0, 25.7 (3C), 24.1, 23.4, 21.7, 18.2, 16.3, −4.7, −5.4; MS (EI) m/z 629 (M^+); HRMS (FAB, m/z) calcd for $C_{34}H_{52}N_2O_7Si$ 629.3622, found 629.3622.

(3*E*)-4-(*N*-{(1*R*)-2-(3,3-Dimethyl-2-oxoazetidinyl)-1-[(4-methoxyphenyl)methyl]-2-oxoethyl}carbamoyl)-1-((1*R*)-1-methylprop-2-enyl)-(1*S*)-but-3-enyl-(2*S*)-2-hydroxy-4-methylpentanoate (5a). The silyl ether **13** (6.0 mg, 9.5 μmol) was dissolved in $CHCl_3$ (1 mL, dried over activated 4 Å molecular sieves). $BF_3{\cdot}Et_2O$ (10 μL, 76.3 μmol) was added via syringe. After 1 h, $CHCl_3$ (5 mL) and saturated aqueous $NaHCO_3$ (2 mL) were added. The organic layers were dried ($MgSO_4$), filtered, and concentrated to provide clean **5a** as an oil (4.4 mg, 88%). ^{1}H NMR δ 7.10−7.08 (d, J = 9 Hz, 2H), 6.83−6.81 (d, J = 9 Hz, 2H), 6.71−6.63 (dt, J = 7, 15 Hz, 1H), 6.07−6.05 (br d, J = 7 Hz, 1H), 5.81−5.77 (d, J = 15 Hz, 1H), 5.71−5.62 (ddd, J = 8, 10, 17 Hz, 1H), 5.36−5.33 (app q, J = 6 Hz, 1H), 5.08−5.02 (m, 2H), 4.97−4.93 (app q, J = 6 Hz, 1H), 4.14−4.12 (br s, 1H), 3.77 (s, 3H), 3.64−3.61 (m, 1H), 3.54−3.49 (m, 1H), 3.16−3.11 (dd, J = 6, 14 Hz, 1H), 3.08−3.03 (m, 2H), 2.95−2.90 (dd, J = 8, 14 Hz, 1H), 2.45−2.40 (m, 3H), 1.91−1.84 (m, 1H), 1.52−1.48 (m, 2H), 1.00−0.99 (d, J = 6.9 Hz, 3H), 0.95−0.93 (d, J = 7 Hz, 3H), 0.94−0.92 (d, J = 7 Hz, 3H); ^{13}C NMR δ 175.4, 169.6, 164.9, 164.3, 158.8, 139.7, 138.4, 130.3 (2C), 127.2, 125.8, 116.6, 114.0 (2C), 76.4, 69.0, 55.2, 54.6, 43.5, 41.1, 36.6 (2C), 36.0, 34.1, 24.5, 23.3, 21.4, 16.2.

Dephenyldesepoxyarenastatin A (14). Alcohol **5a** (4.4 mg, 8.6 μmol) was dissolved in CH_2Cl_2 (2 mL). Bu_4NCN (21 mg, 77.0 μmol) was dissolved in CH_2Cl_2 (2 mL) and both were stirred with flame-activated crushed 4 Å molecular sieves for 1 h. The Bu_4NCN solution was transferred via syringe dropwise to the solution of **5a**. After 16 h, the reaction was filtered through Celite and concentrated. Column chromatography (50:50 to 75:25 EtOAc:hexanes) provided clean product **14** (3.0 mg, 68%). IR (film) 3420, 3300, 2990, 1740, 1675, 1525 cm^{-1}; ^{1}H NMR δ 7.11−7.09 (d, J = 8.6 Hz, 2H), 7.05−7.02 (t, J = 5.7 Hz, 1H), 6.81−6.79 (d, J = 8.6 Hz, 2H), 6.71−6.63 (ddd, J = 5, 10, 15 Hz, 1H), 5.84−5.82 (d, J = 8 Hz, 1H), 5.75−5.71 (d, J = 14 Hz, 1H), 5.69−5.65 (m, 1H), 5.08 (br s, 1H), 5.05−5.04 (d, J = 6 Hz, 1H), 5.02−4.97 (ddd, J = 2, 5, 11 Hz, 1H), 4.94−4.91 (dd, J = 4, 9.5 Hz, 1H), 4.72−4.66 (m, 1H), 3.76 (s, 3H), 3.54−3.47 (m, 1H), 3.47−3.40 (m, 1H), 3.16−3.11 (dd, J = 6, 14 Hz, 1H), 3.03−2.97 (dd, J = 7.6, 14 Hz, 1H), 2.44−2.28 (m, 2H), 1.76−1.66 (m, 1H), 1.48−1.40 (m, 1H), 1.04−1.02 (d, J = 7 Hz, 3H), 0.92−0.90 (d, J = 6.4 Hz, 3H), 0.88−0.87 (d, J = 6.4 Hz, 3H); ^{13}C NMR δ 172.8, 170.82, 170.76, 165.7, 158.5, 141.8, 138.6, 130.2 (2C), 128.5, 124.9, 116.5, 114.1 (2C), 76.8, 71.4, 55.2, 54.3, 42.4, 39.8, 36.1, 35.2, 34.2, 32.5, 24.5, 22.9, 21.5, 16.6; MS (FAB) m/z 515.3 (M^+ + H); HRMS (FAB, m/z) calcd for $C_{28}H_{39}O_7N_2$ (M^+ + H) 515.2757, found 515.2775.

Desepoxyarenastatin A (15).[40,41] Olefin **14** (17 mg, 33 μmol) was dissolved in CH_3CN (0.33 mL) in a dry sealed tube. The solution was flushed with argon and iodobenzene (4.0 mL, 36 μmol), $Pd(OAc)_2$ (1.1 mg, 5.0 μmol), and TEA (46 mL, 330 μmol) were added. The tube was sealed and placed in a 80−85 °C oil bath with vigorous stirring overnight. After 20 h, the solution was filtered and purified by silica gel chromatography to obtain product **15** as a solid (3 mg, 31% based on recovered starting material) and unreacted starting material **14** (6 mg). $[\alpha]_D$ +27 (c 0.80, $CHCl_3$); IR (film) 3365, 3260, 2940, 1725, 1710, 1665 cm^{-1}; ^{1}H NMR δ 7.33−7.15 (m, 5H), 7.11−7.09 (d, J = 8.6 Hz, 2H), 7.05−7.02 (t, J = 5.5 Hz, 1H), 6.81−6.78 (d, J = 8.6 Hz, 2H), 6.73−6.66 (ddd, J = 4.7, 10, 15 Hz, 1H), 6.41−6.37 (d, J = 16 Hz, 1H), 6.03−5.96 (dd, J = 8.8, 16 Hz, 1H), 5.77−5.75 (d, J = 7.9 Hz, 1H), 5.75−5.71 (d, J = 15 Hz, 1H), 5.06−5.01 (ddd, J = 2, 6.6, 11 Hz, 1H), 4.91−4.88 (dd, J = 3.6, 10 Hz, 1H), 4.73−4.67 (m, 1H), 3.76 (s, 3H), 3.54−3.48 (m, 1H), 3.46−3.39 (m, 1H), 3.15−3.11 (dd, J = 6, 14 Hz, 1H), 3.04−2.98 (dd, J = 7.5, 14 Hz, 1H), 2.57−2.52 (m, 3H), 2.39−2.30 (m, 1H), 1.78−1.57 (m, 3H), 1.35−1.27 (m, 1H), 1.13−1.11 (d, J = 6.8 Hz, 3H), 0.73−0.72 (d, J = 6.4 Hz, 3H), 0.70−0.69 (d, J = 6.4 Hz, 3H); ^{13}C NMR δ 172.8, 170.9, 170.8, 165.6, 158.5, 141.7, 136.7, 131.8, 130.2 (2C), 128.6 (2C), 128.5, 127.5, 126.1 (2C), 125.0, 114.1 (2C), 76.6, 71.5, 55.2, 54.3, 42.2, 39.7, 36.4, 35.2, 34.2, 32.4, 24.3, 22.6, 21.2, 17.2; MS (FAB) m/z 591.3 (M^+ + H); HRMS (FAB, m/z) calcd for $C_{34}H_{43}N_2O_4$ (M^+ + H) 591.3070, found 591.3069.

Arenastatin A (2). Olefin **15** (5.0 mg, 8.5 μmol) was reacted as previously reported[40] with dimethyldioxirane[57] to obtain a 2:1 mixture (de was determined by HPLC Phenomenex Hypersil 5μ, C18, 150 × 3.2 mm, 254 nm, 3:2 CH_3CN:H_2O, 0.5 mL/min, retention time β = 7.2 min, α = 7.9 min) of epoxide diastereomers (3.9 mg, 76%). $[\alpha]_D$ +37 (c 0.10, $CHCl_3$).[40]

***tert*-Butyl (2*E*,7*E*)-5-[(2*S*)-4-Methyl-2-(1,1,2,2-tetramethyl-1-silapropoxy)pentanoyloxy]-(5*S*,6*R*)-6-methyl-8-phenylocta-2,7-dienoate (16).** To alcohol **6b**[41] (181 mg, 0.599 mmol) in CH_2Cl_2 (3 mL) at 0 °C under a nitrogen atmosphere were added DMAP (370 mg, 3.028 mmol) and triethylamine (0.43 mL, 3.052 mmol). To the above solution was added acid chloride **7** (5 equiv), obtained from bis-TBS protected L-leucic acid,[55] in CH_2Cl_2 (6 mL) dropwise at 0 °C. After 10 min the solution was brought to room temperature and stirred for 2 h. The reaction mixture was diluted with excess CH_2Cl_2 and washed with water, saturated bicarbonate solution, and brine, dried over sodium sulfate, filtered, and concentrated. The residue was purified by flash column chromatography (5% ethyl acetate−hexanes) to provide **16** (292 mg, 92%) as a colorless oil. $[\alpha]_D$ +19 (c 2.4, $CHCl_3$); IR (film) 2957, 2857, 1751, 1715, 1151 cm^{-1}; ^{1}H NMR δ 7.37−7.23 (m, 5H), 6.80 (dt, 1H, J = 7.4, 15 Hz), 6.43 (d, 1H, J = 16 Hz), 6.08 (dd, 1H, J = 8.5, 16 Hz), 5.82 (d, 1H, J = 14 Hz), 5.10−5.05 (m, 1H), 4.21 (dd, 1H, J = 4.0, 9.2 Hz), 2.66−2.60 (m, 1H), 2.51−2.47 (m, 2H), 1.82−1.71 (m, 1H), 1.57 (ddd, 1H, J = 4.6, 9.2, 14 Hz), 1.49 (s, 9H), 1.44 (ddd, 1H, J = 5.2, 9.4, 14 Hz), 1.13 (d, 3H, J = 6.8 Hz), 0.92 (s, 9H), 0.88 (d, 3H, J = 6.5 Hz), 0.82 (d, 3H, J = 6.7 Hz), 0.09 (s, 3H), 0.05 (s, 3H); ^{13}C NMR δ 174.4, 165.8, 142.6, 137.4, 132.0, 130.7, 128.9 (2C), 127.8, 126.6 (2C), 126.4, 80.7, 75.9, 71.0, 44.8, 41.3, 34.8, 28.5 (3C), 26.1 (3C), 24.4, 23.7, 21.9, 18.6, 17.2, −4.2, −4.9; MS (FAB+, NBA) m/z 531.4 (M^+ + H); HRMS (FAB, m/z) calcd for $C_{31}H_{54}N_1O_5Si_1$ (M^+ + NH_4) 548.3771, found 548.3765.

***N*-{(1*R*)-2-(3,3-Dimethyl-2-oxoazetidinyl)-1-[(4-methoxyphenyl)methyl]-2-oxoethyl}(*tert*-butoxy)carboxamide (20).** To the tyrosine derivative **18**[36] (221 mg, 0.748 mmol) in acetonitrile (4 mL) at 0 °C was added DIEA (0.5 mL, 2.993 mmol) under a nitrogen atmosphere, followed by HBTU (625 mg, 1.646 mmol). To this mixture was added lactam **19**[60−62] (114 mg, 1.122 mmol) in acetonitrile (6 mL) and the solution was stirred at room temperature for 5 h. The reaction was quenched with saturated NH_4Cl solution and the compound was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with water and brine, dried over sodium sulfate, filtered, and concentrated. Flash column chromatography (20% ethyl acetate−hexanes) of the crude material afforded Boc-protected *N*-acylazetidinone **20** (256 mg, 91%) as a colorless crystalline solid. Mp 112−113 °C; $[\alpha]_D$ −37.5 (c 1.46, $CHCl_3$); IR (film) 3365, 1789, 1712, 1513 cm^{-1}; ^{1}H NMR δ 7.11 (d, 2H, J = 8.2 Hz), 6.79 (d, 2H, J = 8.5 Hz), 5.22 (br d, 1H, J = 7.3 Hz), 5.07 (br d, 1H, J = 4.2 Hz), 3.73 (s, 3H), 3.36 ($^1/_2$ ABq, 1H, J = 7.2 Hz), 3.21 ($^1/_2$ ABq, 1H, J = 7.2 Hz), 3.03−2.98 (m, 1H), 2.88−2.82 (m, 1H), 1.36 (s, 9H), 1.30 (s, 3H), 1.22 (s, 3H); ^{13}C NMR δ 171.2, 159.0 (2C), 155.4, 130.9 (2C), 128.0, 114.2 (2C), 80.1, 56.3, 55.6, 51.7, 50.3, 38.1,

28.7 (2C), 21.8, 21.5 (2C); MS (FAB+, NBA) *m/z* 377.2 (M^+ + H); HRMS (FAB, *m/z*) calcd for $C_{20}H_{29}N_2O_5$ (M^+ + H) 377.2076, found 377.2078.

(3*E*)-1-[(2*E*)-3-(*N*-{(1*R*)-2-(3,3-Dimethyl-2-oxoazetidinyl)-1-[(4-methoxyphenyl)methyl]-2-oxoethyl}carbamoyl)-prop-2-enyl]-(1*S*,2*R*)-2-methyl-4-phenylbut-3-enyl-(2*S*)-2-hydroxy-4-methylpentanoate (5b). To Boc protected amino-acylazetidinone **20** (140 mg, 0.372 mmol) was added 4 N HCl in 1,4-dioxane (3 mL) and the solution was stirred at room temperature for 4 h. The volatiles were removed under vacuo and the residue amine hydrochloride salt **8b** was taken to the next step without further purification. To compound **8b** in acetonitrile (2 mL) at 0 °C was added DIEA (0.36 mL, 2.081 mmol) dropwise under a nitrogen atmosphere, followed by HBTU (316 mg, 0.833 mmol). To this solution was added hydroxy acid **17** [obtained by the simultaneous deprotection of the TBS and *tert*-butyl ester groups of **16** (232 mg, 0.437 mmol), using excess trifluoroacetic acid and CH_2Cl_2] in acetonitrile (8 mL) and the solution was stirred for 4 h. The reaction mixture was diluted with ethyl acetate, washed with water, saturated bicarbonate solution, and brine, dried over sodium sulfate, filtered, and concentrated. The crude residue was purified by flash column chromatography (40% ethyl acetate−hexanes) to afford **5b** (148 mg, 58%) as a colorless oil. $[\alpha]_D$ +10 (*c* 1.1, $CHCl_3$); IR (film) 3346, 1790, 1707, 1513 cm^{-1}; ^1H NMR δ 7.34−7.21 (m, 5H), 7.12 (d, 2H, *J* = 8.5 Hz), 6.83 (d, 2H, *J* = 8.5 Hz), 6.76 (dt, 1H, *J* = 7.7, 15 Hz), 6.40 (d, 1H, *J* = 16 Hz), 6.34 (br d, 1H, *J* = 6.8 Hz, N*H*), 6.03 (dd, 1H, *J* = 8.7, 16 Hz), 5.86 (d, 1H, *J* = 15 Hz), 5.42 (br d, 1H, *J* = 6.1 Hz), 5.06−5.01 (m, 1H), 4.14 (br s, 1H), 3.77 (s, 3H), 3.40 (br s, 1H), 3.26 (d, 1H, *J* = 7.3 Hz), 3.10 (dd, 1H, *J* = 6.5, 14 Hz), 3.00 (dd, 1H, *J* = 7.4, 14 Hz), 2.89 (br s, 1H, O*H*), 2.63−2.43 (m, 3H), 1.87−1.79 (m, 1H), 1.50−1.40 (m, 2H), 1.35 (s, 3H), 1.27 (s, 3H), 1.11 (d, 3H, *J* = 6.8 Hz), 0.90 (d, 3H, *J* = 6.5 Hz), 0.83 (d, 3H, *J* = 6.7 Hz); ^{13}C NMR δ 175.9, 171.3, 170.7, 165.3, 159.2, 140.0, 137.3, 132.2, 130.8 (2C), 130.4, 129.0 (2C), 127.9, 127.7, 126.6 (2C), 126.4, 114.4 (2C), 77.0, 69.4, 55.6, 55.2, 51.9, 50.5, 44.0, 41.2, 37.5, 34.7, 24.8, 23.6, 21.8, 21.7, 21.5, 17.3; MS (FAB+, NBA) *m/z* 619.5 (M^+ + H); HRMS (FAB, *m/z*) calcd for $C_{36}H_{47}N_2O_7$ (M^+ + H) 619.3383, found 619.3402.

(3*E*)-1-[(2*E*)-3-(*N*-Methylcarbamoyl)prop-2-enyl]-(1*S*,2*R*)-2-methyl-4-phenylbut-3-enyl-(2*S*)-2-{3-[3-(4-methoxyphenyl)propanoylamino]-2,2-dimethylpropanoyloxy}-4-methylpentanoate (21). To hydroxy compound **5b** (40 mg, 0.065 mmol) in THF (20 mL) was added tetrabutylammonium cyanide (1.7 mg, 0.006 mmol) in THF (1 mL) at room temperature under a nitrogen atmosphere. The solution was stirred for 30 min. The solvent was removed in vacuo and the residue was subjected to silica gel column chromatography (60% ethyl acetate−hexanes) to afford macrolide **21** as a colorless solid (26 mg, 65%). Mp 85−87 °C; $[\alpha]_D$ +31 (*c* 0.55, acetone); IR (film) 3411, 3283 (br), 1747, 1721, 1651 cm^{-1}; ^1H NMR δ 7.35−7.23 (m, 6H), 7.11 (d, 2H, *J* = 8.5 Hz), 6.83 (d, 2H, *J* = 8.5 Hz), 6.80 (ddd, 1H, *J* = 4.0, 11, 15 Hz), 6.42 (d, 1H, *J* = 16 Hz), 6.03 (dd, 1H, *J* = 8.8, 16 Hz), 5.75 (d, 1H, *J* = 15 Hz), 5.60 (d, 1H, *J* = 7.4 Hz), 5.10−5.05 (m, 1H), 4.87 (dd, 1H, *J* = 3.2, 9.9 Hz), 4.78−4.73 (m, 1H), 3.80 (s, 3H), 3.47 (dd, 1H, *J* = 9.1, 13 Hz), 3.13−3.04 (m, 3H), 2.61−2.53 (m, 2H), 2.44−2.34 (m, 1H), 1.72−1.57 (m, 2H), 1.34 (ddd, 1H, *J* = 3.7, 8.8, 12 Hz), 1.24 (s, 3H), 1.17 (s, 3H), 1.14 (d, 3H, *J* = 6.8 Hz), 0.74 (app t, 6H, *J* = 6.0 Hz); ^{13}C NMR δ 178.6, 171.1, 171.0, 165.4, 159.1, 142.7, 137.1, 132.2, 130.6 (3C), 129.0 (2C), 128.6, 128.0, 126.6 (2C), 124.9, 114.6 (2C), 77.4, 71.9, 55.7, 54.8, 46.8, 43.1, 42.7, 39.9, 37.0, 36.0, 24.9, 23.2, 23.1, 23.0, 21.6, 17.8; MS (FAB+, NBA) *m/z* 619.4 (M^+ + H); HRMS (FAB, *m/z*) calcd for $C_{36}H_{47}N_2O_7$ (M^+ + H) 619.3383, found 619.3381.

Dechlorocryptophycin-52 (4). To macrolide **21** (10 mg, 0.016 mmol) in acetone (2 mL) was added dimethyl dioxirane[57] in acetone (2 mL) at room temperature and the solution was stirred for 2 h. The solvent was removed in vacuo. Silica gel column chromatography (60% ethyl acetate−hexanes) of the residue furnished a diastereomeric mixture (β:α = 2:1) of dechlorocryptophycin-52 (**4**; 7 mg, 68%) as a colorless solid. The mixture was separated by reverse-phase HPLC. **4*β***: Mp 119−121 °C; $[\alpha]_D$ +26.7 (*c* 0.62, $CHCl_3$); IR (film) 3411, 3271, 2959, 2931, 1747, 1720, 1651, 1514, 1247, 1147 cm^{-1}; ^1H NMR δ 7.41−7.33 (m, 3H), 7.27−7.22 (m, 3H), 7.10 (d, 2H, *J* = 8.6 Hz), 6.83 (d, 2H, *J* = 8.6 Hz), 6.79 (ddd, 1H, *J* = 4.2, 10, 15 Hz), 5.70 (d, 1H, *J* = 15 Hz), 5.51 (d, 1H, *J* = 7.6 Hz), 5.25−5.21 (m, 1H), 4.84 (dd, 1H, *J* = 3.2, 10 Hz), 4.75 (q, 1H, *J* = 6.6 Hz), 3.80 (s, 3H), 3.70 (s, 1H), 3.48 (dd, 1H, *J* = 9.1, 13 Hz), 3.13−3.03 (m, 3H), 2.94 (d, 1H, *J* = 7.6 Hz), 2.62−2.57 (m, 1H), 2.51−2.42 (m, 1H), 1.82−1.69 (m, 3H), 1.32 (ddd, 1H, *J* = 3.6, 8.9, 12 Hz), 1.24 (s, 3H), 1.18 (s, 3H), 1.16 (d, 3H, *J* = 8.2 Hz), 0.86 (d, 3H, *J* = 6.5 Hz), 0.84 (d, 3H, *J* = 6.5 Hz); ^{13}C NMR δ 178.6, 171.0, 170.9, 165.2, 159.1, 142.2, 137.2, 130.6 (2C), 129.1 (2C), 129.0, 128.5, 126.0 (2C), 125.0, 114.7 (2C), 76.3, 71.6, 63.5, 59.6, 55.7, 54.8, 46.8, 43.2, 41.1, 39.7, 37.3, 35.9, 25.0, 23.3 (2C), 23.1, 21.6, 14.0; MS (FAB+, NBA) *m/z* 635.6 (M^+ + H); HRMS (FAB, *m/z*) calcd for $C_{36}H_{47}N_2O_8$ (M^+ + H) 635.3332, found 635.3351. **4α**: Mp 94−96 °C; $[\alpha]_D$ +29.6 (*c* 0.27, $CHCl_3$); IR (film) 3413, 3275, 2958, 2927, 1749, 1721, 1659, 1514, 1247, 1148 cm^{-1}; ^1H NMR δ 7.40−7.33 (m, 3H), 7.27−7.25 (m, 3H), 7.13 (d, 2H, *J* = 8.6 Hz), 6.86 (d, 2H, *J* = 8.6 Hz), 6.81 (ddd, 1H, *J* = 4.4, 11, 15 Hz), 5.80 (d, 1H, *J* = 15 Hz), 5.54 (d, 1H, *J* = 7.7 Hz), 5.25−5.20 (m, 1H), 4.94 (dd, 1H, *J* = 3.1, 10 Hz), 4.77 (q, 1H, *J* = 6.0 Hz), 3.82 (s, 3H), 3.61 (d, 1H, *J* = 2 Hz), 3.49 (dd, 1H, *J* = 9.0, 13 Hz), 3.15−3.07 (m, 3H), 2.93 (dd, 1H, *J* = 2.0, 7.9 Hz), 2.75−2.57 (m, 2H), 1.84−1.69 (m, 3H), 1.50 (ddd, 1H, *J* = 3.3, 9.0, 12 Hz), 1.26 (s, 3H), 1.20 (s, 3H), 1.07 (d, 3H, *J* = 7.1 Hz), 0.92 (d, 3H, *J* = 6.5 Hz), 0.89 (d, 3H, *J* = 6.5 Hz); ^{13}C NMR δ 178.6, 171.0, 170.9, 165.4, 159.1, 142.6, 137.5, 130.6 (2C), 129.0 (2C), 128.7, 128.5, 125.8 (2C), 125.0, 114.7 (2C), 77.1, 71.8, 63.6, 56.7, 55.7, 54.8, 46.8, 43.2, 41.4, 40.0, 37.2, 36.0, 25.2, 23.5, 23.3, 23.2, 21.8, 13.9; MS (FAB+, NBA) *m/z* 635.6 (M^+ + H); HRMS (FAB, *m/z*) calcd for $C_{36}H_{47}N_2O_8$ (M^+ + H) 635.3332, found 635.3339.

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Supporting Information Available: General experimental details and ^1H NMR and ^{13}C NMR spectra of compounds **4**, **5a**, **5b**, **10**, **12**, **13**, **14**, **16**, **20**, and **21**. This material is available free of charge via the Internet at http://pubs.acs.org.

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