Total Synthesis of Cryptophycins-1, -3, -4, -24 (Arenastatin A), and -29, Cytotoxic Depsipeptides from Cyanobacteria of the Nostocaceae

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A convergent synthesis of cryptophycins has been developed in which (5*S*,6*R*)-5-hydroxy-6-methyl-8-phenylocta-2(*E*),7(*E*)-dienoic acid (A) is coupled with an amino acid segment (B). Two stereoselective routes to A are described, the first employing allylation of an α-homochiral aldehyde and the second using asymmetric crotylation of an achiral aldehyde to establish the two stereogenic centers present in A. The styryl moiety of A was attached either via Stille coupling or through a Wadsworth−Emmons condensation with diethyl benzylphosphonate. The amino acid subunit B was prepared from benzyl (2*S*)-2-hydroxyisocaproate by connection first to *N*-Boc-*β*-alanine or its (2*R*)-methyl-substituted derivative and then to (2*R*)-*N*-Boc-*O*-methyltyrosine or its *m*-chloro derivative. Fusion of the A and B subunits was accomplished by initial esterification of the former with the latter, followed by macrocyclization using diphenyl phosphorazidate. In this way, cryptophycin-3, -4, and -29 were obtained along with the nonnatural cyclic depsipeptide **52**. Epoxidation of cryptophycin-3 with dimethyldioxirane gave cryptophycin-1; analogous epoxidation of **52** afforded arenastatin A (cryptophycin-24).

The cryptophycins are macrocyclic depsipeptides[1] that typically exhibit potent tumor-selective cytotoxicity.[2] For example, cryptophycin-1 (**1**) has an IC_{50} value of 20 pM against SKOV3 human ovarian carcinoma and has shown excellent activity against solid tumors implanted in mice, including a drug-resistant tumor.[3] The first cryptophycin was isolated by a team of scientists at Merck from a blue-green alga (cyanobacterium) belonging to the Nostocaceae.[4] Its structure was established as **1** by Moore et al.,[5] who had isolated this and six additional cytotoxic cryptophycins independently from *Nostoc* sp. GSV 224. Among these were cryptophycins-2 (**2**), -3 (**3**), and -4 (**4**).[6] At approximately the same time, Kitagawa isolated a powerfully cytotoxic depsipeptide that he named arenastatin A from the Okinawan marine sponge *Dysidea arenaria*.[7] This compound was subsequently found to be identical with cryptophycin-24 (**5**) isolated by Moore and has been shown to strongly inhibit tubulin assembly in vitro.[8] A closely related cyclic depsipeptide **6** (cryptophycin-29) was also isolated from this same *Nostoc* species that has now yielded more than 20 members of the cryptophycin family.[3] Structural variation within the subset of macrocyclic cryptophycins is centered on three sites: (a) the styryl residue in **3**, **4**, and **6** that is epoxidized in **1**, **2**, and **5**, (b) the *β*-alanine residue in **5** and **6** that is methylated at the α-carbon in **1**−**4**, and (c) the (*R*)-*O*-methyltyrosinyl residue of **2**, **4**, and **5** that bears a *m*-chloro substituent in **1**, **3**, and **6**. A comprehensive study of in vivo structure−activity relationships among these cryptophycins indicates that all three of these modifications contribute positively to their cytotoxic action.[3]

The first synthesis of a cryptophycin was completed by Kitagawa who prepared both arenastatin A (cryptophycin-24, **5**) and its epoxide stereoisomer.[9] Shortly thereafter, Moore and Tius reported syntheses of "cryptophycins C" (**3**) and "D" (**4**), which resulted in revision of the configuration of **3** (and by correlation that of **1**) at the *O*-methyltyrosinyl moiety to (9′*R*).[5] Syntheses of the four cryptophycin**s 1**−**4** have been described by Lavallée,[10] and Sih has completed syntheses of **1** and **3** by a chemoenzymatic route.[11] Leahy has also synthesized **1** using the chlorohydrin, cryptophycin-8, as precursor to the epoxide.[12] Formal syntheses of **1** and **5** have been claimed by Georg[13] and by Shimizu,[14] each of whom prepared the (5*S*,6*S*)-5-hydroxy-6-methyl-8-phenyl-2(*E*),7(*E*)-octadienoic acid moiety of cryptophycins in stereo-

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(11) Salamonczyk, G. M.; Han, K.; Guo, Z.-W.; Sih, C. *J. Org. Chem.* **1996**, *61*, 6893.

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(13) Ali, S. M.; Georg, G. I. *Tetrahedron Lett.* **1997**, *38*, 1703.

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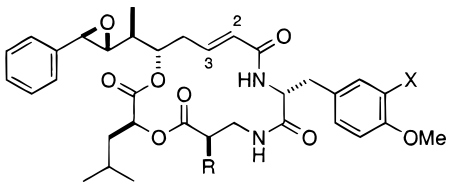
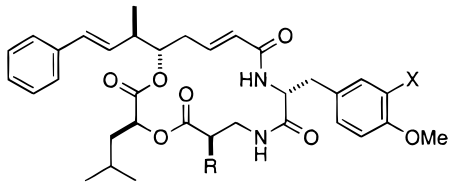


1, R = Me, X = Cl (cryptophycin A, cryptophycin-1)

2, R = Me, X = H (cryptophycin B, cryptophycin-2)

5, R = X = H (arenastatin A, cryptophycin-24)



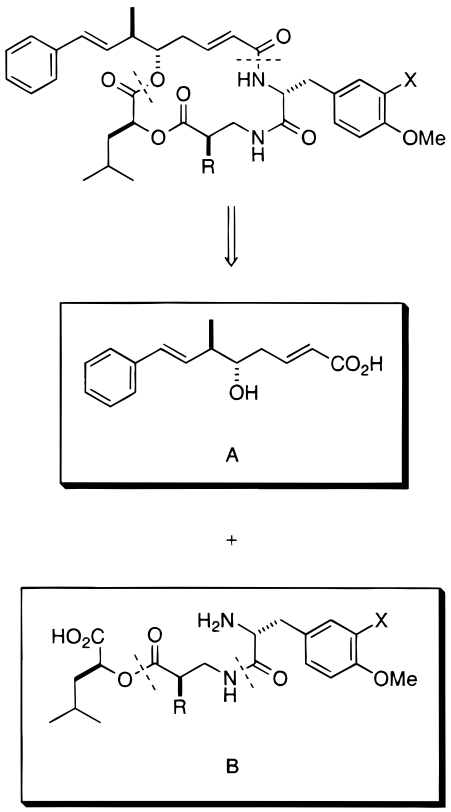
3, R = Me, X = Cl (cryptophycin C, cryptophycin-3)

4, R = Me, X = H (cryptophycin D, cryptophycin-4)

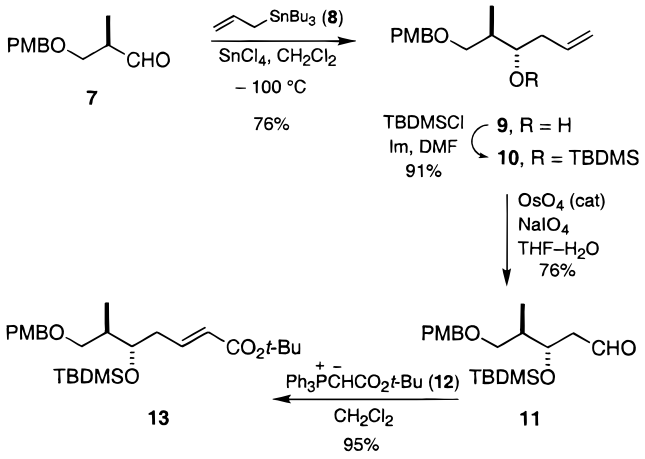
6, R = H, X = Cl (cryptophycin-29)

selective fashion, and recently an improved synthesis of this acid using a [2,3]-Wittig rearrangement was reported.[15] A group at Eli Lilly has actively pursued synthetic analogues of cryptophycins with promising results.[16]

A strategy common to many of the approaches to cryptophycins is one that partitions the structure into two halves, a δ-hydroxy acid (A) and a peptidic subunit (B). The latter is comprised of three segments, (2*S*)-2-hydroxyisocaproate, a β-alanine derivative, and (2*R*)-*O*-methyltyrosine. Our synthesis plan followed the logic implied in this dissection, with the objective of first connecting B to A via an ester linkage before closing the 16-membered ring by macrolactamization. This approach differs from that of Kitagawa's in his synthesis of **5**, where an intramolecular Wadsworth−Emmons condensation was used to close the macrocycle at C2−C3.[8] However, macrolactamization has been favored as the finale in subsequent approaches to cryptophycins,[9−12] including a synthesis of arenastatin A (**5**) previously reported from our laboratories.[17]



Our first route to fragment A began with allylation of (*R*)-aldehyde **7** with stannane **8**. Keck's conditions for this allylation[18] afforded the anti (**9**) and syn homoallylic alcohols in a diastereomeric ratio of 11:1, but decreasing the reaction temperature to −100 °C as recommended by Linderman[19] improved this ratio to 20:1. After purification, **9** was converted to its *tert*-butyldimethylsilyl (TBDMS) ether **10,** which underwent oxidative cleavage of the alkene to yield aldehyde **11**. The latter was subjected to a Wittig reaction with phosphorane **12**[20] and afforded trans α,β-unsaturated *tert*-butyl ester **13** in excellent yield.



Our intention with **13** was to homologate this substance at C7 through a pathway that would create the 7(*E*) olefin of A while permitting incorporation of the terminal aryl substituent in a manner that could accommodate wide structural variation. Although a phenyl group is required for A, other aryl substituents as well as alkyl residues are envisioned as surrogates in prospective cryptophycin analogues. An attractive means for accessing these structural variants appeared to be a Stille coupling,[21] and **13** was therefore advanced in a direction that could be adapted to this strategy.

First, the *p*-methoxybenzyl group was removed from **13** with DDQ in a biphasic solvent system, and the

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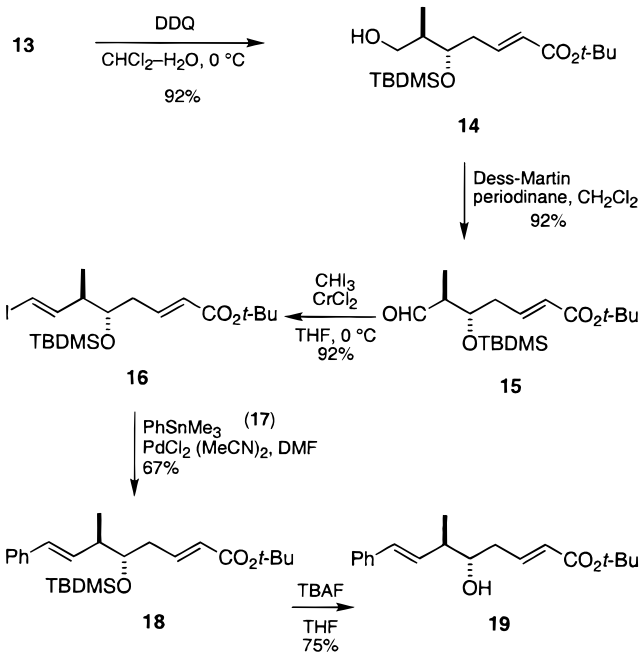
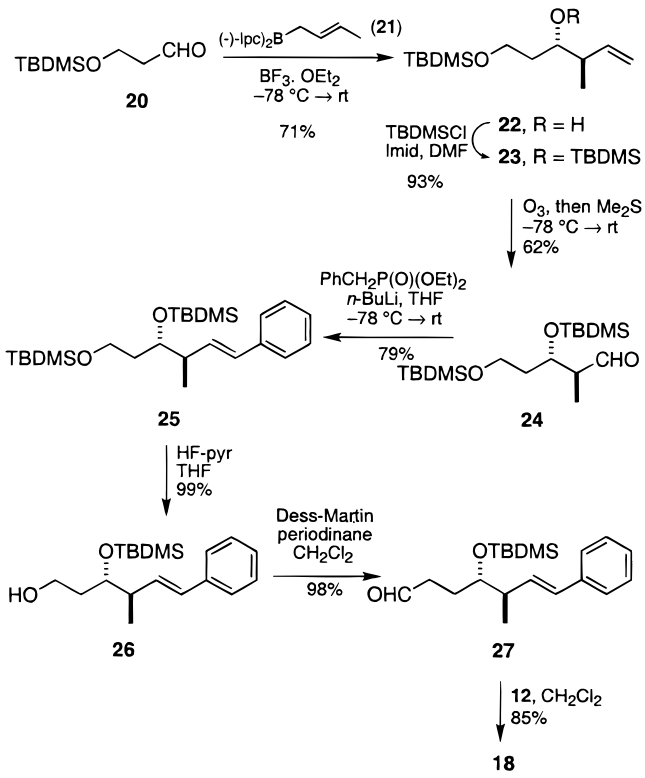
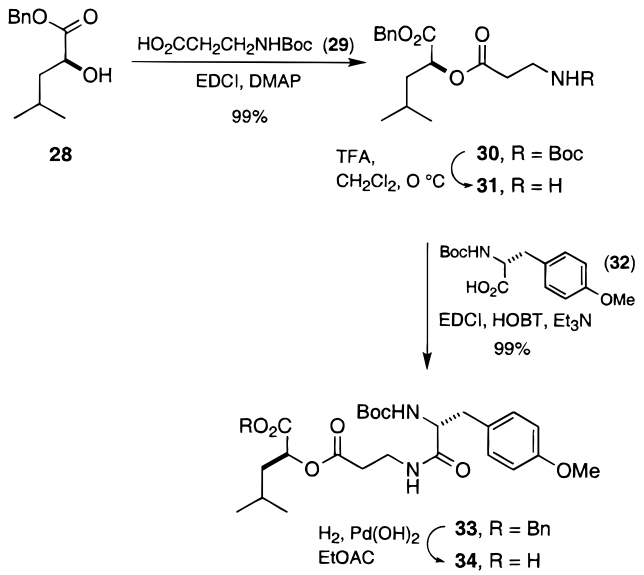
primary alcohol **14** was oxidized to **15**. A Takai reaction[22] of this aldehyde using iodoform gave the (*E*)-iodoalkene **16**, which was coupled to phenyltrimethylstannane (**17**) in the presence of palladium dichloride bisacetonitrile complex.[23] The resultant styrene derivative **18** was then deprotected to furnish hydroxy ester **19**.



Although the nine-step pathway leading from **7** to **19** is relatively efficient (14% yield overall), the need to remove an unwanted stereoisomer from the initial allylation mixture prompted a search for a fully stereoselective method for incorporating the two asymmetric centers of **9**. Reagent-controlled crotylation of an achiral aldehyde in which both diastereo- and enantioselectivity are orchestrated by a chiral element in the nucleophilic partner seemed the best option for achieving this objective. Thus, coupling of the known aldehyde **20**[24] with Brown's (*E*)-crotyldiisopinocampheylborane (**21**),[25] prepared from (+)-diisopinocampheyl(methoxy)borane, yielded the anti homoallylic alcohol **22** with no visible trace of the syn stereoisomer (dr > 50:1). The enantiomeric excess of **22**, as measured on its Mosher ester,[26] was 93%. After conversion of **22** to bis silyl ether **23**, the terminal alkene was cleaved by ozonolysis to furnish aldehyde **24**. Wadsworth–Emmons olefination of **24** with diethylbenzylphosphonate[27] gave alkene **25** as the *E* stereoisomer exclusively. The primary silyl ether of **25** was cleaved selectively and in quantitative yield with HF–pyridine complex, and the resulting primary alcohol **26** was oxidized to aldehyde **27** with Dess–Martin periodinane. Wittig olefination of **27** with phosphorane **12**[20] produced **18**, identical with the substance obtained from **7**. This route afforded hydroxy ester **19** in an overall yield of 20% from **20**.



Segment B was initially prepared in its least substituted version corresponding to the peptidic subunit of arenastatin A (**5**). Benzyl (−)-2-hydroxyisocaproate (**28**)[28] was coupled to *N*-Boc-*β*-alanine (**29**), and the resultant diester **30** was deprotected to give the free amine **31**. The latter was next condensed with *N*-Boc-*O*-methyl-D-tyrosine (**32**), affording **33** in quantitative yield. Subsequent hydrogenolysis of the benzyl ester gave carboxylic acid **34**. Analogous treatment of **31** with *N*-Boc-3-chloro-*O*-



methyl-D-tyrosine (**35**), prepared by chlorination of *N*-acetyl-*O*-methyl-D-tyrosine with sulfuryl chloride[5] followed by protection with Boc anhydride, gave **36**, from which the benzyl ester was removed by hydrogenolysis.

(22) Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 7408.
(23) Stille, J. K.; Groh, B. L. *J. Am. Chem. Soc.* **1987**, *109*, 813.
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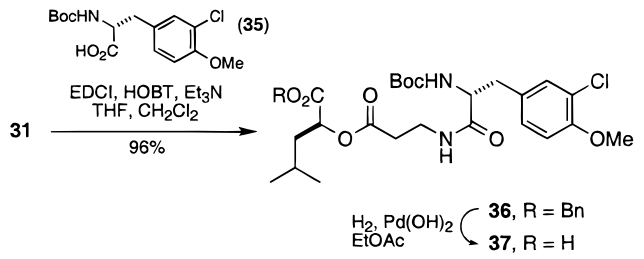
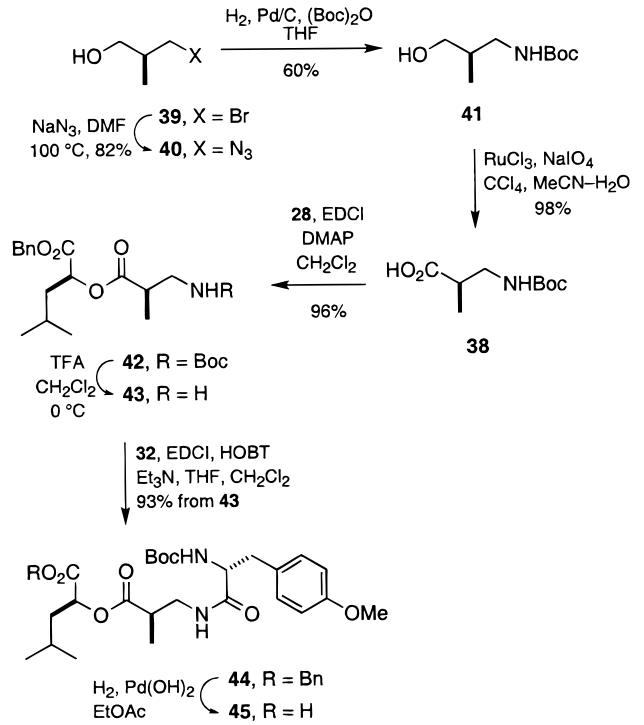
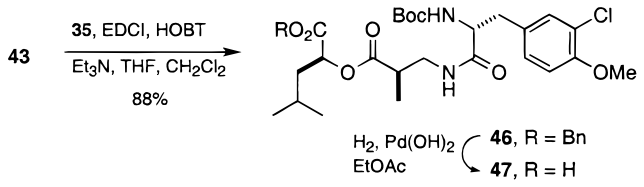
The resultant carboxylic acid **37** represents the peptidic moiety of **6**.



For the synthesis of the peptidic segment corresponding to cryptophycins-1−4 (**1**−**4**), it was necessary to insert a (2*R*)-3-amino-2-methylpropionate subunit in place of *β*-alanine. Synthesis of the requisite N-protected amino acid **38** was accomplished from (2*S*)-3-bromo-2-methylpropanol (**39**) by displacement with sodium azide[10] followed by hydrogenation of the azido alcohol **40** in the presence of Boc anhydride.[29] This furnished the protected amino alcohol **41**, which was then oxidized to **38**. Esterification of **38** with alcohol **28** afforded diester **42**, from which the Boc protection was removed to yield amine **43**. Coupling of **43** to D-tyrosine derivative **32** gave the dipeptide **44**, and hydrogenolysis of this benzyl ester produced carboxylic acid **45**. Analogous coupling of **43**

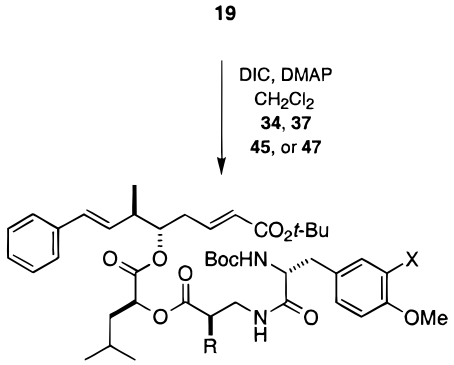


with the chlorinated tyrosine **35** yielded peptide **46**, which was converted to **47** upon hydrogenolysis.

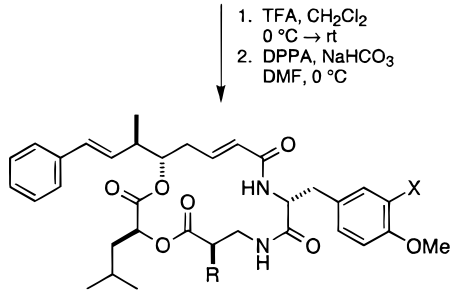


(29) Pearson, A. J.; Shin, H. *J. Org. Chem.* **1994**, *59*, 2314.

The connection of A and B subunits was made through esterification of hydroxy ester **19** successively with carboxylic acids **34**, **37**, **45**, and **47**. This afforded amino ester derivatives **48**−**51**, respectively, in high yield and set the stage for final ring closure via macrolactamization. The Boc protecting group and *tert*-butyl ester of each coupled product were cleaved in a single step with CF_3CO_2H, and the resultant amino acids were immediately activated as their acyl azides.[30] Spontaneous cyclization occurred to give desepoxyarenastatin A (**52**), cryptophycin-3 (**3**), cryptophycin-4 (**4**), and cryptophycin-29 (**6**) from **48**, **51**, **50**, and **49**, respectively. Spectral data (IR, ^{1}H NMR, and ^{13}C NMR) for **3**, **4**, and **6**, were in excellent agreement with those recorded for the natural materials.[3,11]

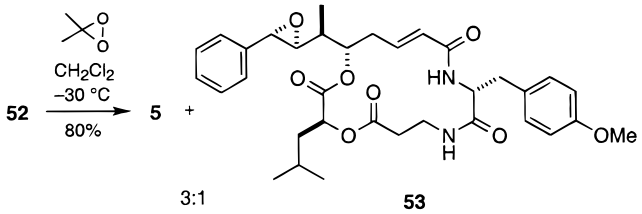


48, R = X = H (93%)
49, R = H, X = Cl (85%)
50, R = Me, X = H (84%)
51, R = Me, X = Cl (89%)



52, R = X = H (57%)
6, R = H, X = Cl (58%)
4, R = Me, X = H (61%)
3, R = Me, X = Cl (52%)

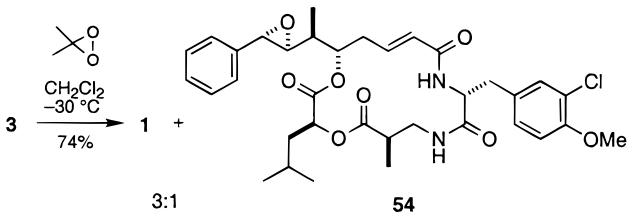
Epoxidation of **52** to arenastatin A (**5**) and its stereoisomer **53** with dimethyldioxirane has been previously reported by Kitagawa to yield a 2.2:1 ratio of **5**:**53**.[7b]



Lowering the temperature of this reaction to −30 °C was found to slightly improve this ratio to 3:1 in favor of **5**.

(30) Shioiri, T.; Ninomiya, K.; Yamada, S. *J. Am. Chem. Soc.* **1972**, *94*, 6203.

The mixture of arenastatin (**5**) and epiarenastatin (**53**) was separated by HPLC, and the major component was shown to be identical spectroscopically with natural arenastatin A.[3] Analogous epoxidation of cryptophycin-3 (**3**) at −30 °C gave cryptophycin-1 (**1**) and its epimer **54**, also in a 3:1 ratio, respectively. After separation, **1** was found to be identical with natural cryptophycin-1 by comparison of spectral data with those published by Sih.[11]



In summary, a modular synthesis of cryptophycins has been demonstrated that allows access to a variety of structures in this class. Interest in these macrocyclic depsipeptides as possible agents for treatment of certain cancers is likely to continue, and versatile synthetic routes to members of this group will play an important role in this area of drug development.

Experimental Section

General Methods. All moisture-sensitive reactions were performed in flame-dried glassware under a dry argon atmosphere. Tetrahydrofuran (THF), diethyl ether (Et_2O), and toluene ($PhCH_3$) were distilled from sodium−benzophenone ketyl. Dichloromethane (CH_2Cl_2), triethylamine (Et_3N), dimethyl sulfoxide (DMSO), and *N*,*N*-dimethylformamide (DMF) were distilled from calcium hydride. All other commercial reagents were purchased and used as received unless otherwise specified. Melting points (mp) are uncorrected. Optical rotations are reported in g/100 mL. Infrared spectra (IR) are reported in wavenumbers (cm^{-1}) with broad signals denoted by (br). High-resolution mass spectra were obtained using chemical ionization (CI) or fast atom bombardment (FAB). Analytical thin-layer chromatography (TLC) was performed using TLC plates precoated with silica gel 60 F-254 (0.25 mm layer thickness). TLC visualization was accomplished using either a UV lamp, iodine adsorbed on silica gel, or phosphomolybdic acid (PMA) solution. Flash chromatography was performed on 320−400-mesh silica gel. Solvent mixtures used for TLC and flash chromatography are reported in $V/V_{total} \times 100$. Reversed-phase preparative HPLC was carried out using an ODS-AQ (S-5 μm, 120 A, 250 × 10 mm i.d.) silica column.

(2*R*,3*S*)-1-(4-Methoxybenzyloxy)-2-methylhex-5-en-3-ol (9). To a cooled (−100 °C) solution of tri-*n*-butylallylstannane (1.95 g, 5.89 mmol) in dry CH_2Cl_2 (12.0 mL) was added dropwise a solution of tin tetrachloride in CH_2Cl_2 (5.89 mL, 1.0 M, 5.89 mmol) at −100 °C. After addition was complete, the solution was stirred for 15 min, and a solution of **7** (754 mg, 3.93 mmol) in CH_2Cl_2 (3.6 mL) was added dropwise via cannula. The mixture was stirred at −100 °C for 1 h and then was quenched by addition of saturated aqueous $NaHCO_3$ solution and was allowed to warm to room temperature. The aqueous layer was extracted with Et_2O, and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash chromatography (silica gel, elution with 20% Et_2O in hexanes) to give 0.747 g (2.99 mmol, 76%) of **9** and its 3*R* stereoisomer (20:1) as a colorless oil: R_f 0.32 (50% Et_2O in hexanes, PMA); $[\alpha]^{22}_D$ −6.46 (*c* 1.30, $CHCl_3$); IR (film) 3463 (br), 2959, 1612, 1513, 1248, 1089, 1036, 820 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.25 (AA′ of AA′BB′, 2H), 6.87 (BB′ of AA′BB′, 2H), 5.88 (m, 1H), 5.10 (m, 2H), 4.45 (s, 2H), 3.80 (s, 3H), 3.57 (m, 2H), 3.44 (dd, 1H, J = 7.1, 9.2 Hz), 3.30 (s, 1H), 2.32 (m, 1H), 2.18 (m, 1H), 1.86 (m, 1H), 0.90 (d, 3H, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 159.2, 135.2, 129.9, 129.2, 117.1, 113.8, 75.0, 74.4, 73.0, 55.2, 39.3, 37.79, 13.78; HRMS (CI, *m*/*z*) calcd for $C_{15}H_{22}O_3$ (M^+) 250.1569, found 250.1565.

***tert*-Butyldimethylsilyl Ether 10.** To a solution of **9** (1.25 g, 5.00 mmol) in dry DMF (16.7 mL) were added imidazole (852 mg, 12.5 mmol) and *tert*-butyldimethylsilyl chloride (1.13 g, 7.51 mmol). The mixture was stirred at room temperature for 18 h, and H_2O was added to quench the reaction. The aqueous layer was extracted with Et_2O, and the organic extract was washed with H_2O and saturated aqueous NaCl solution, dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash chromatography (silica gel, elution with 9% Et_2O in hexanes) to give 1.74 g (4.77 mmol, 95%) of **10** as a colorless oil: R_f 0.61 (50% Et_2O in hexanes, PMA); $[\alpha]^{22}_D$ +14.5 (*c* 1.50, $CHCl_3$); IR (film) 2955, 2928, 2854, 1513, 1248, 1074, 835, 774 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.28 (AA′ of AA′BB′, 2H), 6.90 (BB′ of AA′BB′, 2H), 5.85 (m, 1H), 5.05 (m, 2H), 4.43 (AB_q, 2H, J_{AB} = 11.6 Hz, $\Delta\nu_{AB}$ = 20.8 Hz), 3.82 (s, 3H), 3.74 (m, 1H), 3.48 (m, 1H), 3.31 (m, 2H), 2.22 (m, 2H), 1.98 (m, 1H), 0.95 (d, 3H, J = 7.1 Hz), 0.90 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 159.0, 135.5, 130.9, 129.0, 116.6, 113.7, 73.4, 72.6, 72.1, 55.2, 38.4, 38.2, 25.9, 18.1, 13.3, −4.2, −4.7; HRMS (FAB, *m*/*z*) calcd for $C_{21}H_{37}O_3Si$ (M^+ + H) 365.2513, found 365.2512.

(3*S*,4*R*)-3-*tert*-Butyldimethylsilanyloxy-5-(4-methoxybenzyloxy)-4-methylpentanal (11). To a solution of **10** (235 mg, 0.646 mmol) in THF (17.2 mL) and H_2O (8.6 mL) was added a solution of OsO_4 in *t*-BuOH (2.5 wt %, 0.66 mL, 0.646 mmol). After 15 min, $NaIO_4$ (552 mg, 2.58 mmol) was added, and the mixture was stirred at room temperature for 20 h. The resulting white suspension was filtered and washed with Et_2O, and the filtrate was diluted with 20% $Na_2S_2O_3$ solution. After being stirred for 10 min, the solution was extracted with Et_2O, and the ethereal extract was dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash chromatography (silica gel, elution with 11% Et_2O in hexanes) to give 182 mg (0.496 mmol, 77%) of **11** as a pale yellow oil: R_f 0.55 (50% Et_2O in hexanes, PMA); $[\alpha]^{22}_D$ −4.43 (*c* 1.31, $CHCl_3$); IR (film) 2954, 2928, 2854, 1726, 1613, 1513, 1463, 1249, 1085, 1036, 837, 776 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 9.76 (t, 1H, J = 2.3 Hz), 7.23 (AA′ of AA′BB′, 2H), 6.87 (BB′ of AA′BB′, 2H), 4.50 (AB_q, 2H, J_{AB} = 11.7 Hz, $\Delta\nu_{AB}$ = 21.7 Hz), 4.33 (m, 1H), 3.78 (s, 3H), 3.31 (m, 2H), 2.46 (m, 2H), 2.05 (m, 1H), 0.90 (d, 3H, J = 7.0 Hz), 0.87 (s, 9H), 0.074 (s, 3H), 0.051 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 202.2, 159.1, 130.3, 129.0, 113.6, 72.6, 71.6, 68.9, 55.1, 47.0, 39.3, 25.7, 17.9, 12.0, −4.7, −4.7; HRMS (CI, *m*/*z*) calcd for $C_{20}H_{33}O_4Si$ (M^+ − H) 365.2148, found 365.2141.

***tert*-Butyl (5*S*,6*R*)-5-*tert*-Butyldimethylsilanyloxy-7-(4-methoxybenzyloxy)-6-methylhept-2(*E*)-enoate (13).** To a solution of **11** (521 mg, 1.42 mmol) in CH_2Cl_2 (4.0 mL) was added (*tert*-butoxycarbonylmethylene)triphenylphosphorane (**12**, 1.07 g, 2.85 mmol). The mixture was stirred at room temperature for 20 h, after which time the solvent was removed in vacuo. The residue was purified by flash chromatography (silica gel, elution with 9% Et_2O in hexanes) to give 627 mg (1.35 mmol, 95%) of **13** as a pale yellow oil: R_f 0.67 (50% Et_2O in hexanes, PMA); $[\alpha]^{22}_D$ +10.2 (*c* 2.0, $CHCl_3$); IR (film) 2955, 2928, 2855, 1714, 1513, 1249, 1153, 1078, 836, 775 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.24 (AA′ of AA′BB′, 2H), 6.86 (m, 3H), 5.73 (d, 1H, J = 15.5 Hz), 4.40 (AB_q, 2H, J_{AB} = 11.6 Hz, $\Delta\nu_{AB}$ = 20.1 Hz), 3.82 (m, 1H), 3.80 (s, 3H), 3.42 (dd, 1H, J = 6.3, 9.3 Hz), 3.28 (dd, 1H, J = 6.3, 9.3 Hz), 2.27 (m, 2H), 1.95 (m, 1H), 1.48 (s, 9H), 0.90 (d, 3H, J = 6.9 Hz), 0.88 (s, 9H), 0.036 (s, 3H), 0.03 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.7, 159.1, 145.1, 130.7, 129.1, 125.0, 113.7, 79.9, 72.6, 71.9, 55.2, 39.0, 36.1, 29.7, 28.1, 25.8, 18.0, 12.8, −4.4, −4.7; HRMS (FAB, *m*/*z*) calcd for $C_{26}H_{44}O_5Si$ (M^+) 464.2958, found 464.2958.

***tert*-Butyl (5*S*,6*R*)-5-*tert*-Butyldimethylsilanyloxy-7-hydroxy-6-methylhept-2(*E*)-enoate (14).** To a cooled (0 °C) solution of **13** (1.24 g, 2.67 mmol) in CH_2Cl_2 (37.9 mL) and H_2O (3.8 mL) was added DDQ (1.21 g, 5.35 mmol) in one portion. The mixture was stirred at 0 °C for 0.5 h and then was allowed to warm to room temperature during 0.5 h. The reaction was quenched with saturated aqueous $NaHCO_3$

solution, and the aqueous layer was extracted with CH_2Cl_2. The organic extract was dried ($MgSO_4$), filtered, and concentrated in vacuo, and the residue was purified by flash chromatography (silica gel, gradient elution with 17% and 25% Et_2O in hexanes) to give 849 mg (2.47 mmol, 92%) of **14** as a colorless oil: R_f 0.31 (50% Et_2O in hexanes, PMA); $[\alpha]^{22}_D$ +20.2 (*c* 1.08, $CHCl_3$); IR (film) 3453 (br), 2956, 2929, 2856, 1715, 1367, 1255, 1157, 1076, 1039, 837, 775 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.76 (dt, 1H, J = 7.6, 15.6 Hz), 5.70 (d, 1H, J = 15.5 Hz), 3.76 (dt, 1H, J = 5.1, 5.8 Hz), 3.60 (dd, 1H, J = 4.8, 10.9 Hz), 3.48 (dd, 1H, J = 5.7, 10.9 Hz), 2.73 (s, 1H), 2.34 (m, 2H), 1.70 (m, 1H), 1.40 (s, 9H), 0.89 (d, 3H, J = 7.0 Hz), 0.83 (s, 9H), 0.018 (s, 3H), 0.009 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.5, 143.9, 125.2, 80.0, 74.8, 64.7, 39.3, 37.1, 28.0, 25.7, 17.8, 13.6, −4.5, −4.8; HRMS (CI, *m*/*z*) calcd for $C_{18}H_{37}O_4Si$ (M^+ + H) 345.2461, found 345.2458.

***tert*-Butyl (5*S*, 6*S*)-5-*tert*-Butyldimethylsilanyloxy-6-methyl-7-oxohept-2(*E*)-enoate (15).** To a cooled (0 °C) solution of **14** (198 mg, 0.576 mmol) in CH_2Cl_2 (5.76 mL) was added Dess−Martin periodinane (488 mg, 1.15 mmol) in one portion, and the mixture was stirred at room temperature for 3 h. The solvent was removed in vacuo, and the residue was diluted with Et_2O and saturated aqueous $NaHCO_3$ solution. The aqueous layer was extracted with Et_2O, and the organic extract was dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash chromatography (silica gel, elution with 13% Et_2O in hexanes) to give 181 mg (0.528 mmol, 92%) of **15** as a colorless oil: R_f 0.55 (50% Et_2O in hexanes, PMA); $[\alpha]^{22}_D$ +45.3 (*c* 1.62, $CHCl_3$); IR (film) 2955, 2930, 2857, 1717, 1665, 1256, 1156, 837, 777 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 9.74 (d, 1H, J = 2.2 Hz), 6.83 (dt, 1H, J = 7.5, 15.6 Hz), 5.78 (d, 1H, J = 15.6 Hz), 4.03 (q, 1H, J = 5.6 Hz), 2.53 (m, 1H), 2.40 (m, 2H), 1.48 (s, 9H), 1.09 (d, 3H, J = 7.1 Hz), 0.88 (s, 9H), 0.072 (s, 3H), 0.057 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 204.3, 165.4, 142.8, 126.1, 80.3, 72.5, 51.1, 37.6, 28.1, 25.7, 18.0, 10.4, −4.3, −5.8; HRMS (CI, *m*/*z*) calcd for $C_{18}H_{33}O_4Si$ (M^+ − H) 341.2148, found 341.2141.

***tert*-Butyl (5*S*,6*R*)-5-*tert*-Butyldimethylsilanyloxy-8-iodo-6-methylocta-2(*E*),7(*E*)-dienoate (16).** To a stirred suspension of anhydrous $CrCl_2$ (388 mg, 3.16 mmol) in dry THF (5.26 mL) under Ar at 0 °C were added dropwise a solution of **15** (180 mg, 0.526 mmol) and iodoform (415 mg, 1.05 mmol) in THF (2.63 mL). After being stirred at 0 °C for 3 h, the reaction was quenched with H_2O, and the aqueous layer was extracted with Et_2O. The organic extract was dried ($MgSO_4$), filtered, and concentrated in vacuo, and the residue was purified by flash chromatography (silica gel, elution with 2% Et_2O in hexanes) to give 152 mg (0.326 mmol, 62%) of **16** as a colorless oil: R_f 0.46 (9% Et_2O in hexanes, PMA); $[\alpha]^{22}_D$ +58.6 (*c* 1.66, $CHCl_3$); IR (film) 2955, 2928, 2856, 1714, 1665, 1366, 1255, 1154, 1092, 837, 775 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.77 (dt, 1H, J = 7.4, 15.7 Hz), 6.46 (dd, 1H, J = 8.6, 14.6 Hz), 6.02 (d, 1H, J = 4.1 Hz), 5.73 (d, 1H, J = 5.5 Hz), 3.61 (dt, 1H, J = 4.4, 6.0 Hz), 2.27 (m, 3H), 1.47 (s, 9H), 0.98 (d, 3H, J = 6.9 Hz), 0.88 (s, 9H), 0.036 (s, 3H), 0.030 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.5, 147.9, 143.9, 125.3, 80.1, 75.7, 74.1, 45.924, 37.4, 28.1, 25.8, 18.0, 15.6, −4.4, −4.5; HRMS (CI, *m*/*z*) calcd for $C_{19}H_{34}O_3SiI$ (M^+ − H) 465.1322, found 465.1303.

***tert*-Butyl (5*S*,6*R*)-*trans*-5-*tert*-Butyldimethylsilanyloxy-6-methyl-8-phenylocta-2(*E*),7(*E*)-dienoate (18).** To a mixture of **16** (40.0 mg, 0.0858 mmol) and bis(acetonitrile)-dichloropalladium(II) (1.2 mg, 0.00215 mmol) in dry DMF (degassed, 0.80 mL) was added phenyltrimethyltin (**17**, 31 mg, 0.129 mmol). The mixture was stirred in the dark at room temperature for 20 h, and the reaction was quenched with 10% $NaHCO_3$ solution. The aqueous layer was extracted with Et_2O, and the organic extract was washed with H_2O and saturated aqueous NaCl solution, dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash chromatography (silica gel, elution with 2.5% Et_2O in hexanes) to give 23.9 mg (0.0575 mmol, 67%) of **18** as a colorless oil: R_f 0.34 (9% Et_2O in hexanes, PMA); $[\alpha]^{22}_D$ +79.9 (*c* 1.66, $CHCl_3$); IR (film) 2956, 2928, 2856, 1714, 1655, 1256, 1155, 1097, 836, 775 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.20−7.38 (m, 5H), 6.86 (dt, 1H, J = 7.6, 15.5 Hz), 6.40 (d, 1H, J = 16.0 Hz), 6.18 (dd, 1H, J = 8.1, 16.0 Hz), 5.75 (d, 1H, J = 15.5 Hz), 3.76 (dt, 1H, J = 4.0, 6.3 Hz), 2.48 (m, 1H), 2.34 (m, 2H), 1.49 (s, 9H), 1.12 (d, 3H, J = 6.9 Hz), 0.93 (s, 3H), 0.081 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.7, 144.8, 137.6, 132.0, 130.4, 128.4, 127.0, 126.0, 125.1, 80.0, 75.1, 42.8, 37.2, 28.1, 25.8, 18.1, 16.0, −4.4, −4.5; HRMS (CI, *m*/*z*) calcd for $C_{25}H_{39}O_3Si$ (M^+ − H) 415.2668, found 415.2667; calcd for $C_{25}H_{41}O_3Si$ (M^+ + H) 417.2825, found 417.2793.

***tert*-Butyl (5*S*,6*R*)-5-Hydroxy-6-methyl-8-phenylocta-2(*E*),7(*E*)-dienoate (19).** To a solution of **18** (54.0 mg, 0.130 mmol) in THF (1.85 mL) was added tetra-*n*-butylammonium fluoride hydrate (TBAF, 102 mg, 0.389 mmol), and the mixture was stirred at room temperature for 4.5 h. The solvent was removed in vacuo, and the residue was purified by flash chromatography (silica gel, gradient elution with 17% and 25% Et_2O in hexanes) to give 28.9 mg (0.0957 mmol, 75%) of **19** as a colorless oil: R_f 0.28 (50% Et_2O in hexanes, PMA); $[\alpha]^{22}_D$ +62.2 (*c* 0.83, $CHCl_3$); IR (film) 3453 (br), 2974, 2929, 2856, 1712, 1651, 1367, 1154, 980 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.20−7.40 (m, 5H), 6.93 (dt, 1H, J = 7.2, 15.8 Hz), 6.47 (d, 1H, J = 15.9 Hz), 6.14 (dd, 1H, J = 8.6, 15.9 Hz), 5.84 (d, 1H, J = 15.8 Hz), 3.65 (dt, 1H, J = 2.5, 4.1 Hz), 2.30−2.48 (m, 3H), 1.86 (br, 1H), 1.48 (s, 9H), 1.15 (d, 3H, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.7, 144.0, 137.0, 131.5, 131.0, 128.5, 127.6, 126.2, 125.4, 80.2, 73.8, 43.2, 37.2, 28.1, 16.7; HRMS (CI, *m*/*z*) calcd for $C_{19}H_{25}O_3$ (M^+ − H) 301.1804, found 301.1799.

(3*S*,4*R*)-1-*tert*-Butyldimethylsilanyloxy-4-methylhex-5-en-3-ol (22). To a cooled (−78 °C) suspension of potassium *tert*-butoxide (4.20 g, 37.4 mmol) in dry THF (40 mL) under Ar was added *trans*-2-butene (6.70 mL, 74.2 mmol) via cannula, followed by *n*-butyllithium (1.60 M in hexanes, 25.0 mL, 40.0 mmol). The resulting yellow mixture was stirred at −45 °C for 0.5 h and then was cooled to −78 °C. A solution of (+)-*B*-methoxydiisopinocampheylborane (12.0 g, 37.97 mmol) in THF (40.0 mL) was added via cannula, and the mixture was stirred for 1 h. $BF_3{\cdot}Et_2O$ (5.10 mL, 40.0 mmol) was introduced slowly, and the solution was stirred for 0.5 h, after which time a solution of **20** (5.10 g, 27.1 mmol) in THF (40.0 mL) was added via cannula. The mixture was stirred at −78 °C for 4 h, quenched with 3 N NaOH (50.0 mL) at −78 °C followed by a 30% solution of H_2O_2 (50.0 mL), and was allowed to warm to room temperature. The aqueous layer was extracted with Et_2O, and the organic extract was washed with brine, dried ($MgSO_4$), filtered, concentrated, and purified by flash chromatography (silica gel, elution with 12% Et_2O in hexanes) to give 4.70 g (19.3 mmol, 71%) of **22** as a colorless oil: R_f 0.49 (15% Et_2O in hexanes, PMA); $[\alpha]^{22}_D$ +7.74 (*c* 1.55, $CHCl_3$); IR (film) 3453, 3076, 2955, 2928, 2856, 1471, 1255 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.82 (m, 1H), 5.0−5.1 (m, 2H), 3.92−3.75 (m, 2H), 3.68 (m, 1H), 3.20 (s, 1H), 2.23 (m, 1H), 1.62 (m, 1H), 1.04 (d, 3H, J = 6.6 Hz), 0.89 (s, 9H), 0.06 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 140.7, 115.1, 75.0, 62.7, 43.9, 35.5, 25.8, 18.1, 15.7, −5.6, −5.5; HRMS (CI, *m*/*z*) calcd for $C_{13}H_{29}O_2Si$ (M^+ + H) 245.1937, found 245.1934.

(3*S*,4*R*)-1-*tert*-Butyldimethylsilanyloxy-3-methylhex-1-ene (23). To a rapidly stirred solution of **22** (3.60 g, 14.8 mmol) in DMF (30.0 mL) was added imidazole (2.01 g, 29.5 mmol) followed by *tert*-butyldimethylsilyl choloride (2.89 g, 19.2 mmol). The resulting mixture was stirred at room temperature until TLC showed complete comsumption of starting material, and the reaction was quenched by the addition of water (30 mL). The aqueous layer was extracted with Et_2O, and the organic extract was washed with brine. The organic solution was dried ($MgSO_4$), filtered, and concentrated in vacuo, and the residue was purified by chromatography (silica gel, elution with 7% EtOAc in hexanes) to give 4.91 g (13.7 mmol, 97%) of **23**: R_f 0.35 (7% EtOAc in hexanes, PMA); $[\alpha]^{22}_D$ +7.74 (*c* 1.55, $CHCl_3$); IR (film) 2953, 2926, 2855, 1472, 1255, 1099, 836, 774 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.78 (ddd, 1H, J = 7.4, 9.6, 17.4 Hz), 5.02 (m, 1H), 4.97 (m, 1H), 3.74 (dt, 1H, J = 3.7, 6.1 Hz), 3.63 (q, 2H, J = 6.5 Hz), 2.30 (m, 1H), 1.58 (q, 2H, J = 6.4 Hz), 1.00 (d, 3H, J = 6.8 Hz), 0.89 (s, 9H), 0.88 (s, 9H), 0.051 (s, 6H), 0.035 (s, 6H); ^{13}C

NMR ($CDCl_3$, 75 MHz) δ 140.8, 114.3, 72.3, 60.1, 43.3, 36.3, 25.9, 25.7, 18.2, 18.1, 14.7, −4.5, −5.3; HRMS (CI, *m*/*z*) calcd for $C_{19}H_{41}O_2Si_2$ ($M^+ - H$) 357.2645, found 357.2649.

(2*S*,3*S*)-3,5-Bis(*tert*-butyldimethylsilanyloxy)-2-methylpentanal (24). Ozone was bubbled through a stirred solution of **23** (500 mg, 1.40 mmol) in CH_2Cl_2 (47 mL) at −78 °C until a light blue color persisted. After the reaction was complete, Ar was bubbled through the solution until it became colorless. Dimethyl sulfide (2.60 mL, 34.9 mmol) was added via syringe at −78 °C, and the mixture was allowed to slowly warm to room temperature. The solvent was removed in vacuo, and the residue was purified by flash chromatography (silica gel, elution with 5% Et_2O in hexanes) to give 302 mg (0.840 mmol, 62%) of **24** as a colorless oil: R_f 0.29 (5% Et_2O in hexanes, PMA); $[\alpha]^{22}_D$ +22.9 (*c* 1.77, $CHCl_3$); IR (film) 2955, 2929, 2857, 1727, 1471, 1256, 1099 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 9.73 (d, 1H, J = 2.0 Hz), 4.14 (q, 1H), 3.69 (t, 2H, J = 6.2 Hz), 2.54 (m, 1H), 1.82−1.56 (m, 2H), 1.10 (d, 3H, J = 7.1 Hz), 0.88 (s, 18H), 0.76 (s, 3H), 0.63 (s, 3H), 0.04 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 204.8, 70.4, 59.1, 51.5, 37.6, 25.9, 25.8, 18.2, 18.0, 10.2, −4.4, −4.8, −5.4; HRMS (CI, *m*/*z*) calcd for $C_{18}H_{40}O_3Si_2$ ($M^+ - H$) 359.2436, found 359.2438.

(3*R*,4*S*)-[4,6-Bis(*tert*-butyldimethylsilanyloxy)-3-methylhex-1(*E*)-enyl]benzene (25). To a cooled (−78 °C) solution of diethyl benzylphosphonate (0.253 mL, 1.22 mmol) in dry THF (4.0 mL) under Ar was added *n*-BuLi, (1.60 M in hexane, 0.607 mL, 0.972 mmol). After 15 min, a solution of **24** (219 mg, 0.610 mmol) in THF (1.5 mL) was added via cannula, and the mixture was stirred at −78 °C for 2 h. The mixture was allowed to warm to room temperature, and the reaction was quenched with H_2O. After dilution with Et_2O, the mixture was extracted with Et_2O, and the organic extract was washed with brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash chromatography (silica gel, elution with 5% Et_2O in hexanes) to give 212 mg (0.490 mmol, 79%) of **25** as a colorless oil: R_f 0.63 (5% Et_2O in hexanes, PMA); $[\alpha]^{22}_D$ +24.6 (*c* 1.84, $CHCl_3$); IR (film) 2954, 2927, 2855, 1471, 1255, 1098 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.265−7.39 (m, 4H), 7.20 (m, 1H), 6.35 (d, 1H, J = 16.1 Hz), 6.19 (dd, 2H, J = 7.7, 16.0 Hz), 3.86 (m, 1H), 3.68 (m, 2H), 2.48 (m, 1H), 1.65 (q, 2H, J = 6.5 Hz), 1.11 (d, 3H, J = 6.8 Hz), 0.92 (s, 9H), 0.89 (s, 9H), 0.08 (s, 6H), 0.044 (s, 3H), 0.041 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 137.8, 132.8, 129.8, 128.4, 126.8, 126.0, 72.7, 60.1, 42.7, 36.7, 25.9, 18.3, 18.1, 15.5, −4.5, −5.3; HRMS (CI, *m*/*z*) calcd for $C_{25}H_{46}O_2Si_2$ ($M^+ - H$) 433.2956, found 433.2958.

(3*S*,4*R*)-3-*tert*-Butyldimethylsilanyloxy-4-methyl-6-phenylhex-5(*E*)-en-1-ol (26). A solution of HF−pyridine was prepared by addition of 13.0 g of HF−pyridine to pyridine (31 mL) and THF (100 mL). This solution (3.82 mL) was added to a solution of **25** (272 mg, 0.627 mmol) in THF (11.4 mL) via syringe, and the mixture was stirred for 18 h at room temperature. The reaction was quenched by addition of saturated $NaHCO_3$ solution, and the aqueous layer was extracted with Et_2O. The organic extract was washed with brine, dried ($MgSO_4$), filtered, and concentrated in vacuo, and the residue was purified by flash chromatography (silica gel, elution with 15% EtOAc in hexanes) to give 194 mg (0.61 mmol, 97%) of **26** as a colorless oil: R_f 0.22 (15% EtOAc in hexanes, PMA); $[\alpha]^{22}_D$ +28.8 (*c* 2.59, $CHCl_3$); IR (film) 3360 (br), 2954, 2927, 2855, 1471, 1255, 1098 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.26−7.39 (m, 4H), 7.20 (m, 1H), 6.38 (d, 1H, J = 16.0 Hz), 6.19 (dd, 2H, J = 7.7, 16.0 Hz), 3.90 (m, 1H), 3.75 (m, 2H), 2.56 (m, 1H), 1.97 (s, 1H), 1.73 (q, 2H, J = 5.7, 12.3 Hz), 1.10 (d, 3H, J = 6.7 Hz), 0.92 (s, 9H), 0.11 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 137.5, 132.6, 130.0, 128.5, 127.0, 126.0, 74.6, 60.5, 42.7, 35.0, 25.9, 18.0, 14.8, −4.3, −4.6; HRMS (CI, *m*/*z*) calcd for $C_{19}H_{32}O_2Si$ ($M^+ - H$) 319.2092, found 319.2093.

(3*S*,4*R*)-3-*tert*-Butyldimethylsilanyloxy-4-methyl-6-phenylhex-5(*E*)-enal (27). To a cooled (0 °C) solution of **26** (193 mg, 0.604 mmol) in dry CH_2Cl_2 (6.04 mL) was added Dess−Martin periodinane (536 mg, 1.21 mmol). The mixture was stirred at room temperature for 1 h and was treated with 10 mL of saturated $NaHCO_3$ solution and 10 mL of 20% aqueous $Na_2S_2O_3$ solution. The aqueous layer was extracted with Et_2O, and the organic extract was washed with brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash chromatography (silica gel, elution with 15% EtOAc in hexanes) to give 189 mg (0.59 mmol, 98%) of **27** as a colorless oil: R_f 0.41 (15% EtOAc in hexanes, PMA); $[\alpha]^{22}_D$ +43.4 (*c* 1.99 $CHCl_3$); IR (film) 2954, 2927, 1724, 1253, 1096 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 9.80 (t, 1H), 7.26−7.39 (m, 4H), 7.20 (m, 1H), 6.40 (d, 1H, J = 16.0 Hz), 6.13 (dd, 2H, J = 7.7, 16.0 Hz), 4.26 (m, 1H), 2.6−2.5 (m, 3H), 1.14 (d, 3H, J = 7.0 Hz), 0.91 (s, 9H), 0.13 (s, 3H), 0.08 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 201.9, 137.3, 131.3, 130.9, 128.5, 127.2, 126.1, 71.3, 48.1, 43.3, 25.8, 18.0, 15.2, −4.5, −4.6; HRMS (CI, *m*/*z*) calcd for $C_{19}H_{29}O_2Si$ ($M^+ - H$) 317.1935, found 317.1937.

***tert*-Butyl (5*S*,6*R*)-5-*tert*-Butyldimethylsilanyloxy-6-methyl-8-phenylocta-2(*E*),7(*E*)-dien-oate (18).** To a solution of **27** (48.5 mg, 0.153 mmol) in dry CH_2Cl_2 (3.0 mL) was added (*tert*-butoxycarbonylmethylene)triphenylphosphorane (**12**, 287 mg, 0.763 mmol). The mixture was stirred at room temperature for 18 h and was concentrated in vacuo. The residue was purified by flash chromatography (silica gel, elution with 15% EtOAc in hexanes) to give 54.1 mg (130 mmol, 85%) of **18**, identical with material prepared from **16**.

Benzyl (2*S*)-2-(3-*tert*-Butoxycarbonyaminopropionyloxy)-4-methylpentanoate (30). To a cooled (0 °C) solution of benzyl (−)-2-hydroxyisocaproate (**28**, 111 mg, 0.50 mmol) and *N*-Boc-β-alanine (**29**, 142 mg, 0.75 mmol) in CH_2Cl_2 (2.5 mL) were added 4-(dimethylamino)pyridine (DMAP, 92.0 mg, 0.75 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI, 144 mg, 0.75 mmol), and the mixture was stirred at room temperature for 18 h. The solvent was removed in vacuo, and the residue was purified by flash chromatography (silica gel, elution with 20% Et_2O in hexanes) to give 195 mg (0.496 mmol, 99%) of **30** as a colorless oil: R_f 0.43 (50% Et_2O in hexanes, PMA); $[\alpha]^{22}_D$ −28.1 (*c* 1.34, $CHCl_3$); IR (film) 3394 (br), 2974, 2960, 1742, 1714, 1250, 1169 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.35 (m, 5H), 5.14 (m, 4H), 3.41 (m, 2H), 2.57 (t, 2H, J = 6.4 Hz), 1.60−1.72 (m, 3H), 1.42 (s, 9H), 0.93 (d, 3H, J = 5.6 Hz), 0.90 (d, 3H, J = 5.7 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.9, 170.5, 155.7, 135.1, 128.5, 128.4, 128.1, 79.2, 71.1, 67.0, 39.5, 36.2, 34.5, 28.3, 24.5, 22.9, 21.4; HRMS (CI, *m*/*z*) calcd for $C_{21}H_{36}NO_6$ ($M^+ + H$) 394.2230, found 394.2218.

Benzyl (2*S*)-2-[3-[(2*R*)-2-*tert*-Butoxycarbonylamino-3-(4-methoxyphenyl)propionylamino]-propionyloxy]-4-methylpentanoate (33). A solution of **30** (100 mg, 0.255 mmol) in CH_2Cl_2 (1.25 mL) at 0 °C was treated with CF_3CO_2H (1.20 mL), and the mixture was stirred at 0 °C for 1 h. The solvent was removed in vacuo, and the residue (123 mg) was dried by azeotropic removal of H_2O with toluene. The crude material was subjected to the next reaction without further purification.

To a cooled (0 °C) solution of the crude amine−TFA salt (123 mg, 0.255 mmol) and *N*-Boc-*O*-methyl-D-tyrosine (**32**, 123 mg, 0.331 mmol) in THF (2.5 mL) and CH_2Cl_2 (0.5 mL) were added 1-hydroxybenzotriazole (HOBT, 34.5 mg, 0.255 mmol), Et_3N (62.0 mg, 0.0850 mL, 0.611 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI, 63.4 mg, 0.331 mmol). The mixture was stirred at 0 °C for 0.5 h and then was allowed to warm to room temperature and was stirred for 18 h. The solvent was removed in vacuo, and the residue was purified by flash chromatography (silica gel, elution with 25% EtOAc in hexanes) to give 144 mg (0.252 mmol, 99%) of **33** as a colorless oil: R_f 0.29 (50% EtOAc in hexanes, PMA); $[\alpha]^{22}_D$ −26.3 (*c* 1.03, $CHCl_3$); IR (film) 3321 (br), 2955, 2930, 1740, 1659, 1513, 1247, 1170 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.32 (m, 5H), 7.07 (d, 2H, J = 8.1 Hz), 6.77 (d, 2H, J = 8.4 Hz), 6.72 (br. 1H), 5.12 (m, 4H), 4.31 (s, 3H), 3.72 (s, 3H), 3.67−3.46 (m, 2H), 2.95 (m, 2H), 2.52 (m, 2H), 1.70 (m, 3H), 1.37 (s, 9H), 0.90 (d, 3H, J = 5.6 Hz), 0.88 (d, 3H, J = 5.7 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.2, 170.6, 158.3, 155.1, 134.9, 130.1, 128.5, 128.3, 128.0, 113.7, 79.5, 71.0, 67.0, 55.6, 55.0, 39.3, 37.8, 34.9, 33.9, 28.1, 24.4, 22.7, 21.4; HRMS (CI, *m*/*z*) calcd for $C_{31}H_{43}N_2O_8$ ($M^+ + H$) 571.3019, found 571.3007.

(2*S*)-2-[3-[(2*R*)-2-*tert*-Butoxycarbonylamino-3-(4-methoxyphenyl)propionylamino]propionyloxy]-4-methylpentanoic Acid (34). To a solution of **33** (20.0 mg, 0.0351 mmol) in EtOAc (0.5 mL) was added $Pd(OH)_2$ (20% on carbon, 2.5 mg, 0.00351 mmol), and the mixture was stirred vigorously at room temperature under a H_2 atmosphere for 2 h. The mixture was filtered, and the filtrate was concentrated in vacuo. The residue (17.0 mg) was dried by azeotropic removal of H_2O with toluene to leave crude **34**, which was subjected to the next reaction without further purification: $[\alpha]^{22}_D$ −0.89 (*c* 1.81, $CHCl_3$); IR (film) 3316 (br), 2959, 2925, 1733, 1714, 1514, 1248, 1176 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, mixture of rotamers) δ 8.90 (bs, 1H), 7.07 (d, 2H, J = 7.2 Hz), 6.77 (d, 2H, J = 8.6 Hz), 5.45 (m, 1H), 5.05 (m, 1H), 4.26 (m, 1H), 3.73 (s, 3H), 3.62 (m, 1H), 3.45 (m, 2H), 2.92 (m, 2H), 2.48 (m, 2H), 1.72 (m, 3H), 1.36 (s, 9H), 0.91 (d, 3H, J = 5.9 Hz), 0.88 (d, 3H, J = 5.9 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.8, 171.6, 158.4, 155.7, 130.2, 128.5, 113.8, 80.3, 77.2, 71.6, 55.7, 55.1, 39.6, 37.7, 35.2, 34.0, 29.6, 28.2, 24.7, 23.0, 21.4; HRMS (FAB, *m*/*z*) calcd for $C_{24}H_{37}N_2O_8$ (M^+ + H) 481.2550, found 481.2555.

***tert*-Butyl (5*S*,6*R*)-5-[(2*S*)-2-[3-[(2*R*)-2-*tert*-Butoxycarbonylamino-3-(4-methoxyphenyl)- propionylamino]propionyloxy]-4-methylpentanoyloxy]-6-methyl-8-phenylocta-2(*E*),7(*E*)-dienoate (48).** To a solution of **19** (28.9 mg, 0.0957 mmol) and **34** (77.0 mg, 0.144 mmol) in CH_2Cl_2 (0.8 mL) was added 4-(dimethylamino)pyridine (DMAP, 17.6 mg, 0.144 mmol). To this solution was slowly added 1,3-diisopropylcarbodiimide (DIC, 18.1 mg, 0.0225 mL, 0.144 mmol), and the mixture was stirred at room temperature for 18 h. The solvent was removed in vacuo, and the residue was purified by flash chromatography (silica gel, gradient elution with 20% and 50% Et_2O in hexanes) to give 68.2 mg (0.0849 mmol, 93%) of **48** as a colorless oil: R_f 0.26 (50% EtOAc in hexanes, PMA); $[\alpha]^{22}_D$ +2.24 (*c* 1.70, $CHCl_3$); IR (film) 3355 (br), 2960, 2867, 1741, 1711, 1666, 1513, 1248, 1167, 756 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.20−7.30 (m, 5H), 7.12 (d, 2H, J = 8.6 Hz), 6.80 (d, 2H, J = 8.6 Hz), 6.74 (br, 1H), 6.42 (d, 1H, J = 15.9 Hz), 6.02 (dd, 1H, J = 8.6, 15.8 Hz), 5.83 (d, 1H, J = 15.6 Hz), 5.42 (br, 1H), 5.04 (m, 1H), 4.96 (dd, 1H, J = 4.0, 9.8 Hz), 4.34 (m, 1H), 3.75 (s, 3H), 3.52 (m, 2H), 3.13 (dd, 1H, J = 5.4, 13.8 Hz), 2.93 (m, 1H), 2.43−2.62 (m, 5H), 1.65 (m, 3H), 1.48 (s, 9H), 1.35 (s, 9H), 1.10 (d, 3H, J = 6.8 Hz), 0.84 (d, 3H, J = 6.5 Hz), 0.79 (d, 3H, J = 6.5 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.5, 171.3, 170.7, 165.7, 158.4, 155.4, 141.7, 136.8, 131.7, 130.3, 130.0, 129.1, 128.5, 127.4, 126.1, 113.8, 80.4, 79.5, 76.6, 76.4, 71.2, 55.8, 40.9, 39.6, 37.8, 35.1, 34.7, 34.2, 29.6, 28.2, 28.1, 24.5, 22.8, 21.3, 16.9; HRMS (FAB, *m*/*z*) calcd for $C_{43}H_{61}N_2O_{10}$ (M^+ + H) 765.4326, found 765.4319.

Desepoxyarenastatin A (52). To a solution of **48** (68.0 mg, 0.0891 mmol) in CH_2Cl_2 (1.27 mL) at 0 °C was slowly added CF_3CO_2H (5.09 mL), and the mixture was allowed to warm to room temperature and was stirred for 2 h. The solvent was removed in vacuo, and the residue (84.9 mg) was dried by azeotropic removal of H_2O with toluene. This material was subjected to the next reaction without further purification.

To a cooled (0 °C) solution of the crude amine−TFA salt (84.9 mg, 0.0891 mmol) in dry DMF (11.1 mL) were added $NaHCO_3$ (45.0 mg, 0.535 mmol) and diphenyl phosphorazidate (DPPA, 36.8 mg, 0.029 mL, 0.134 mmol), and the mixture was stirred at 0 °C for 72 h. The reaction was quenched by addition of H_2O, and the aqueous layer was extracted with EtOAc, CH_2Cl_2, and EtOAc. The combined organic extract was washed with H_2O, dried ($MgSO_4$), filtered, and concentrated in vacuo, and the residue was purified by flash chromatography (silica gel, gradient elution with 50% EtOAc in hexanes, 17% and 25% acetone in hexanes) to give 30.0 mg (0.051 mmol, 57%) of **52** as a colorless oil: R_f 0.33 (50% acetone in hexanes, PMA); $[\alpha]^{22}_D$ +34.0 (*c* 1.36, CH_2Cl_2); mp 250−251 °C; IR (film) 3282 (br), 2957, 2926, 1741, 1731, 1674, 1513, 1247, 1176, 971 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.18−7.35 (m, 5H), 7.12 (d, 2H, J = 8.5 Hz), 7.00 (br, 1H), 6.80 (d, 1H, J = 8.5 Hz), 6.71 (ddd, 1H, J = 4.5, 10.2, 15.3 Hz), 6.40 (d, 1H, J = 15.8 Hz), 6.02 (dd, 1H, J = 8.8, 15.8 Hz), 5.74 (d, 1H, J = 15.3 Hz), 5.67 (d, 1H, J = 8.2 Hz), 5.04 (m, 1H), 4.90 (dd, 1H, J = 3.5, 9.5 Hz), 4.74 (m, 1H), 3.77 (s, 3H), 3.46 (m, 2H), 3.15 (dd, 1H, J = 5.6, 14.3 Hz), 3.04 (dd, 1H, J = 7.4, 14.3 Hz), 2.35−2.55 (m, 4H), 1.60−1.75 (m, 3H), 1.33 (m, 1H), 1.13 (d, 3H, J = 6.7 Hz), 0.74 (d, 3H, J = 6.4 Hz), 0.71 (d, 3H, J = 6.4 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.8, 170.7, 165.5, 158.5, 141.5, 136.7, 131.8, 130.2, 128.6, 127.5, 126.1, 125.1, 114.1, 77.2, 71.5, 55.2, 54.1, 42.3, 39.7, 36.4, 35.2, 34.2, 34.4, 29.7, 24.3, 22.6, 21.2, 17.3; HRMS (FAB, *m*/*z*) calcd for $C_{34}H_{43}N_2O_7$ (M^+ + H) 591.3070, found 591.3065.

Arenastatin A (5). To a cooled (−30 °C) solution of **52** (20.0 mg, 0.0339 mmol) in CH_2Cl_2 (1.18 mL) was added a solution of dimethyldioxirane in acetone (1.0 mL, 0.06 M, 0.060 mmol) dropwise at −30 °C. The mixture was stirred at −30 °C for 6 h, after which time an additional quantity (1.0 mL, 0.06M, 0.060 mmol) of dimethyldioxirane−acetone solution was added. The mixture was stirred at −30 °C for a further 18 h and then was allowed to warm to room temperature. The solvent was removed in vacuo, and the residue (20 mg) was dissolved in CH_2Cl_2 (0.2 mL) and MeOH (0.3 mL) and was purified by reversed-phase HPLC (YMC−Pack ODS-AQ, S-5 μm, 120 A, 250 × 10 mm i.d.; UV dectection at 254 nm, MeOH/H_2O = 75:25, flow rate 3.5 mL/min) to afford arenastatin A (**5**, t_R = 17.92 min) and its epimer (**53**, t_R = 19.77 min) in MeOH−H_2O. Removal of MeOH from each fraction in vacuo gave **5** (12.3 mg, 0.0202 mmol, 60%) and **53** (4.0 mg, 0.00658 mmol, 20%) as colorless solids. Data for **5**: R_f 0.29 (50% acetone in hexanes, PMA); $[\alpha]^{22}_D$ +48.7 (*c* 0.87, $CHCl_3$) (lit.[3] $[\alpha]^{22}_D$ +48.8 (*c* 0.63, $CHCl_3$)); IR (film) 3404, 3282, 2964, 2930, 1738, 1670, 1514, 1240, 1176, 756 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.36 (m, 3H), 7.26 (m, 2H), 7.10 (d, 2H, J = 8.6 Hz), 6.99 (t, 1H, J = 6.0 Hz), 6.80 (d, 2H, J = 8.7 Hz), 6.70 (ddd, 1H, J = 4.8, 10.3, 15.1 Hz), 5.70 (dd, 1H, J = 1.2, 15.2 Hz), 5.63 (d, 1H, J = 8.1 Hz), 5.20 (m, 1H), 4.90 (dd, 1H, J = 3.6, 9.9 Hz), 4.70 (m, 1H), 3.77 (s, 3H), 3.68 (d, 1H, J = 2.0 Hz), 3.40−3.50 (m, 2H), 3.14 (dd, 1H, J = 4.7, 14.4 Hz), 3.02 (dd, 1H, J = 7.6, 14.4 Hz), 2.92 (dd, 1H, J = 1.8, 7.4 Hz), 2.20−2.55 (m, 4H), 1.70 (m, 3H), 1.14 (d, 3H, J = 7.0 Hz), 0.84 (d, 3H, J = 6.4 Hz), 0.83 (d, 3H, J = 6.4 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.8, 170.6, 165.3, 158.5, 141.1, 136.7, 130.2, 128.7, 128.5, 128.4, 125.6, 125.2, 114.1, 77.2, 75.8, 71.2, 63.0, 59.0, 55.2, 54.1, 40.6, 39.5, 36.7, 35.2, 34.2, 32.4, 24.4, 22.8, 21.2, 13.5; HRMS (FAB, *m*/*z*) calcd for $C_{34}H_{43}N_2O_8$ (M^+ + H) 607.3019, found 607.3022.

Data for **53**: R_f 0.29 (50% acetone in hexanes, PMA); $[\alpha]^{22}_D$ +34.5 (*c* 0.40, $CHCl_3$); IR (film) 3394, 3282, 2960, 2925, 1738, 1679, 1250, 1176, 756 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.33 (m, 3H), 7.23 (m, 2H), 7.12 (d, 2H, J = 8.4 Hz), 7.03 (m, 1H), 6.80 (d, 2H, J = 8.4 Hz), 6.70 (m, 1H), 5.77 (m, 2H), 5.18 (m, 1H), 4.98 (m, 1H), 4.73 (m, 1H), 3.78 (s, 3H), 3.59 (d, 1H, J = 1.3 Hz), 3.48 (m, 2H), 3.16 (dd, 1H, J = 5.5, 14.4 Hz), 3.04 (dd, 1H, J = 7.4, 14.2 Hz), 2.90 (dd, 1H, J = 6.3, 7.5 Hz), 2.55−2.65 (m, 4H), 1.76 (m, 3H), 1.05 (d, 3H, J = 6.9 Hz), 0.89 (d, 3H, J = 6.4 Hz), 0.87 (d, 3H, J = 6.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.8, 170.8, 165.6, 158.6, 141.4, 137.1, 130.2, 128.6, 128.3, 125.4, 125.2, 114.1, 76.7, 75.5, 71.4, 65.8, 63.2, 56.3, 55.2, 54.2, 40.9, 39.5, 36.6, 35.2, 34.2, 32.5, 24.6, 23.0, 21.4, 15.2, 13.4; HRMS (FAB, *m*/*z*) calcd for $C_{34}H_{43}N_2O_8$ (M^+ + H) 607.3019, found 607.3026.

***tert*-Butyl (2*R*)-(3-Hydroxy-2-methylpropyl)carbamate (41).** A solution of **39** (500 mg, 3.26 mmol) and NaN_3 (426 mg, 6.55 mmol) in DMF (3.4 mL) was heated at 100 °C for 4 h. After being cooled to room temperature, the mixture was filtered, and the solids were washed with Et_2O. The filtrate was washed with H_2O and saturated aqueous NaCl solution, dried ($MgSO_4$), filtered, and concentrated in vacuo to give crude **40** as a colorless oil (307 mg, 2.67 mmol, 82%).

To a solution of **40** (100 mg, 0.870 mmol) and Boc_2O (285 mg, 1.31 mmol) in THF (4.3 mL) was added 10% Pd on carbon (99.0 mg), and the mixture was stirred at room temperature for 36 h under a H_2 atmosphere. The mixture was filtered through a pad of silica gel that was thoroughly washed with EtOAc, and the filtrate was concentrated in vacuo. The residue was purified by flash chromatography (silica gel, elution with 50% Et_2O in hexanes) to give 98.5 mg (0.521 mmol, 60%) of **41** as a colorless oil: R_f 0.27 (50% EtOAc in hexanes, PMA); $[\alpha]^{22}_D$ −12.9 (*c* 1.93, $CHCl_3$); IR (film) 3349 (br), 2974, 2930,

2881, 1687, 1525, 1173 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.12 (br, 1H), 3.66 (br. 1H), 3.48 (m, 1H), 3.30 (m, 1H), 3.13 (m, 1H), 2.97 (dt, 1 H, $J = 6.5, 13.2$ Hz), 1.72 (m, 1H), 1.37 (s, 9H), 0.81 (d, 3H, $J = 7.0$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 157.3, 79.4, 64.3, 42.6, 36.1, 28.2, 14.3; HRMS (CI, *m*/*z*) calcd for $C_9H_{20}NO_3$ ($M^+ + H$) 190.1443, found 190.1442.

Benzyl (2*S*)-2-((2*R*)-3-*tert*-Butoxycarbonylamino-2-methylpropionyloxy)-4-methylpentanoate (42). To a solution of **41** (97.0 mg, 0.513 mmol) and $NaIO_4$ (328 mg, 1.53 mmol) in CCl_4 (1.06 mL), CH_3CN (1.06 mL), and H_2O (1.64 mL) was added ruthenium(III) chloride trihydrate (13.4 mg, 0.0511 mmol). The mixture was stirred at room temperature for 2.5 h, diluted with CH_2Cl_2, dried ($MgSO_4$), filtered, and concentrated in vacuo. The resulting crude **38** (103 mg, 0.510 mmol, 99%) was used for the next reaction without further purification.

To a cooled (0 °C) solution of **28** (75.6 mg, 0.340 mmol) and **38** (103 mg, 0.510 mmol) in CH_2Cl_2 (1.70 mL) were added 4-(dimethylamino)pyridine (DMAP, 62.3 mg, 0.510 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI, 97.8 mg, 0.510 mmol), and the mixture was stirred at room temperature for 18 h. The solvent was removed in vacuo, and the residue was diluted with Et_2O, washed with H_2O and saturated aqueous NaCl solution, dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash chromatography (silica gel, elution with 14% Et_2O in hexanes) to give 133 mg (0.327 mmol, 96%) of **42** as a colorless oil: R_f 0.44 (50% Et_2O in hexanes, PMA); $[\alpha]^{22}_D$ −49.7 (*c* 1.50, $CHCl_3$); IR (film) 3394 (br), 2960, 1740, 1717, 1509, 1251, 1172 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.32 (m, 5H), 5.16 (m, 4H), 3.37 (m, 1H), 3.20 (m, 1H), 2.74 (m, 1H), 1.62−1.84 (m, 3H), 1.41 (s, 9H), 1.15 (d, 3H, $J = 8.2$ Hz), 0.91 (d, 3H, $J = 6.2$ Hz), 0.89 (d, 3H, $J = 6.2$ Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 174.6, 170.5, 155.9, 135.1, 128.5, 128.3, 128.2, 79.1, 70.8, 67.0, 43.0, 40.2, 39.6, 28.2, 24.6, 22.9, 21.4, 14.4; HRMS (CI, *m*/*z*) calcd for $C_{22}H_{34}NO_6$ ($M^+ + H$) 408.2386, found 408.2377; calcd for $C_{22}H_{32}NO_6$ ($M^+ - H$) 406.2230, found 406.2227.

Benzyl (2*S*)-2-[(2*R*)-3-[(2*R*)-2-*tert*-Butoxycarbonylamino-3-(3-chloro-4-methoxyphenyl) propionylamino]-2-methylpropionyloxy]-4-methylpentanoate (46). To a solution of **42** (133 mg, 0.327 mmol) in CH_2Cl_2 (1.63 mL) at 0 °C was added CF_3CO_2H (1.63 mL), and the mixture was stirred at 0 °C for 1 h. The solvent was removed in vacuo, and the residue (169 mg) was dried by azeotropic removal of H_2O with toluene. Crude **43** was subjected to the next reaction without further purification.To a cooled (0 °C) solution of crude **43** (169 mg, 0.327 mmol) and *N*-Boc-*O*-methyl-D-3-chlorotyrosine (52.7 mg, 0.160 mmol) in THF (1.28 mL) and CH_2Cl_2 (0.32 mL) were added 1-hydroxybenzotriazole (HOBT, 32.4 mg, 0.240 mmol), Et_3N (40.5 mg, 0.0560 mL, 0.400 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI, 61.4 mg, 0.320 mmol). The mixture was stirred at 0 °C for 0.5 h and then was allowed to warm to room temperature and was stirred for a further 18 h. The solvent was removed in vacuo, and the residue was diluted with Et_2O. The ethereal solution was washed with H_2O, and the organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash chromatography (silica gel, elution with 50% Et_2O in hexanes) to give 87.5 mg (0.142 mmol, 88%) of **46** as a colorless oil: R_f 0.41 (50% EtOAc in hexanes, PMA); $[\alpha]^{22}_D$ −32.0 (*c* 1.22, $CHCl_3$); IR (film) 3306 (br), 2955, 2935, 1739, 1655, 1503, 1257, 1172 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.32 (m, 5H), 7.18 (d, 1H, $J = 1.7$ Hz), 7.01 (dd, 1H, $J = 1.9, 8.3$ Hz), 6.91 (br. 1H), 6.78 (d, 1H, $J = 8.5$ Hz), 5.16 (m, 4H), 4.32 (m, 1H), 3.82 (s, 3H), 3.63 (m, 1H), 3.16 (ddd, 1H, $J = 5.0, 9.3, 13.9$ Hz), 3.00 (dd, 1H, $J = 6.4, 13.9$ Hz), 2.93 (m, 1H), 2.74 (m, 1H), 1.60−1.80 (m, 3H), 1.37 (s, 9H), 1.13 (d, 3H, $J = 7.1$ Hz), 0.90 (d, 3H, $J = 6.8$ Hz), 0.88 (d, 3H, $J = 6.8$ Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.7, 171.1, 155.1, 153.7, 134.8, 131.0, 129.9, 128.5, 128.5, 128.1, 122.0, 112.0, 79.7, 70.7, 67.4, 56.0, 55.6, 41.6, 40.2, 39.2, 37.8, 28.1, 24.6, 22.8, 21.4, 14.5; HRMS (CI, *m*/*z*) calcd for $C_{31}H_{43}N_2O_8$ ($M^+ + H$) 619.2786, found 619.2776.

***tert*-Butyl (5*S*,6*R*)-5-[(2*S*)-2-[(2*R*)-3-[(2*R*)-2-*tert*-Butoxycarbonylamino-3-(3-chloro-4-methoxyphenyl)propionylamino]-2-methylpropionyloxy]-4-methylpentanoyloxy]-6-methyl-8-phenylocta-2(*E*),7(*E*)-dienoate (51).** To a solution of **46** (87.5 mg, 0.142 mmol) in EtOAc (2.0 mL) was added $Pd(OH)_2$ (20% on carbon, 10 mg, 0.0142 mmol), and the mixture was stirred vigorously at room temperature under a H_2 atmosphere for 2 h. The mixture was filtered, and the filtrate was concentrated in vacuo. The residue of crude **19** (80.2 mg) was dried by azeotropic removal of H_2O with toluene and was subjected to the next reaction without further purification.To a solution of crude **19** (30.2 mg, 0.106 mmol) and **47** (80.2 mg, 0.142 mmol) in CH_2Cl_2 (0.88 mL) was added DMAP (19.4 mg, 0.159 mmol), followed slowly by 1,3-diisopropylcarbodiimide (DIC, 20.0 mg, 0.025 mL, 0.159 mmol), and the mixture was stirred at room temperature for 18 h. The solvent was removed in vacuo, and the residue was purified by flash chromatography (silica gel, gradient elution with 17% and 25% EtOAc in hexanes) to give 76.8 mg (0.0946 mmol, 89%) of **51** as a colorless oil: R_f 0.37 (50% EtOAc in hexanes, PMA); $[\alpha]^{22}_D$ −4.7 (*c* 4.50, $CHCl_3$); IR (film) 3336 (br), 2976, 2935, 1738, 1732, 1714, 1670, 1504, 1372, 1258, 1168, 756 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.18−7.32 (m, 6H), 7.10 (dd, 1H, $J = 2.1, 8.4$ Hz), 7.05 (m, 1H), 6.82 (d, 1H, $J = 8.4$ Hz), 6.80 (m, 1H), 6.40 (d, 1H, $J = 15.8$ Hz), 6.00 (dd, 1H, $J = 8.7, 15.8$ Hz), 5.82 (d, 1H, $J = 15.6$ Hz), 5.76 (m, 1H), 5.05 (m, 1H), 4.97 (dd, 1H, $J = 3.6, 9.8$ Hz), 4.36 (m, 1H), 3.83 (s, 3H), 3.70 (m, 1H), 3.20 (m, 2H), 2.85 (m, 1H), 2.38−2.68 (m, 4H), 1.50−1.70 (m, 3H), 1.47 (s, 9H), 1.34 (s, 9H), 1.13 (d, 3H, $J = 7.9$ Hz), 1.11 (d, 3H, $J = 6.9$ Hz), 0.83 (d, 3H, $J = 6.3$ Hz), 0.77 (d, 3H, $J = 6.3$ Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.5, 171.8, 171.0, 165.8, 155.7, 153.6, 141.7, 136.7, 131.8, 131.1, 130.6, 129.9, 128.5, 127.4, 126.1, 122.0, 112.1, 80.4, 79.7, 76.6, 70.7, 63.8, 56.0, 42.1, 41.0, 40.6, 39.5, 37.4, 34.9, 29.6, 28.2, 28.1, 24.7, 22.8, 21.2, 16.9, 14.5; HRMS (FAB, *m*/*z*) calcd for $C_{44}H_{62}N_2O_{10}{}^{35}Cl$ ($M^+ + H$) 813.4093, found 813.4104.

Cryptophycin 3 (3). To a solution of **51** (76.0 mg, 0.0936 mmol) in CH_2Cl_2 (1.33 mL) at 0 °C was slowly added CF_3CO_2H (5.35 mL), and the mixture was allowed to warm to room temperature. After the mixture was stirred for 2 h, the solvent was removed in vacuo and the residue (75.1 mg) was dried by azeotropic removal of H_2O with toluene. To a solution of the crude amine−TFA salt (75.1 mg, 0.0936 mmol) in dry DMF (11.7 mL) at 0 °C were added $NaHCO_3$ (47.2 mg, 0.562 mmol) and diphenyl phosphorazidate (DPPA, 38.7 mg, 0.0303 mL, 0.141 mmol), and the mixture was stirred at 0 °C for 72 h. The reaction was quenched with H_2O, and the aqueous layer was extracted with EtOAc, CH_2Cl_2, and EtOAc again. The combined organic extract was washed with H_2O, dried ($MgSO_4$), filtered, and concentrated in vacuo, and the residue was purified by flash chromatography (silica gel, gradient elution with 50% EtOAc in hexanes, 17% and 25% acetone in hexanes) to give 31.0 mg (0.0486 mmol, 52%) of **3** as a colorless oil: R_f 0.39 (50% acetone in hexanes, PMA); $[\alpha]^{22}_D$ +29.5 (*c* 2.0, $CHCl_3$) (lit.[9] $[\alpha]^{22}_D$ +28.8 (*c* 0.65, $CHCl_3$)); IR (film) 3409 (br), 3287 (br), 2964, 2925, 1745, 1730, 1674, 1503, 1181, 1064, 750 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.20−7.35 (m, 6H), 7.06 (dd, 1H, $J = 2.0, 8.5$ Hz), 7.00 (m, 1H), 6.82 (d, 1H, $J = 8.4$ Hz), 6.68 (ddd, 1H, $J = 5.2, 9.7, 15.2$ Hz), 6.40 (d, 1H, $J = 15.8$ Hz), 6.00 (dd, 1H, $J = 8.8, 15.9$ Hz), 5.86 (d, 1H, $J = 8.4$ Hz), 5.78 (d, 1H, $J = 15.4$ Hz), 5.02 (m, 1H), 4.82 (m, 2H), 3.85 (s, 3H), 3.46 (m, 1H), 3.31 (m, 1H), 3.13 (dd, 1H, $J = 5.6, 14.5$ Hz), 3.00 (dd, 1H, $J = 7.6, 14.5$ Hz), 2.70 (m, 1H), 2.54 (m, 2H), 2.37 (m, 1H), 1.57−1.68 (m, 3H), 1.32 (m, 1H), 1.21 (d, 3H, $J = 7.2$ Hz), 1.12 (d, 3H, $J = 6.8$ Hz), 0.75 (d, 3H, $J = 6.4$ Hz), 0.71 (d, 3H, $J = 6.3$ Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 175.6, 171.0, 170.9, 165.5, 153.9, 141.4, 136.7, 131.8, 131.0, 130.1, 129.9, 128.6, 128.4, 127.6, 126.1, 125.2, 122.4, 112.2, 77.4, 71.5, 56.1, 53.7, 42.2, 41.1, 39.5, 38.2, 36.4, 35.1, 24.5, 21.2, 17.3, 14.1; HRMS (FAB, *m*/*z*) calcd for $C_{35}H_{44}N_2O_7{}^{35}Cl$ ($M^+ + H$) 639.2837, found 639.2840.

Cryptophycin-1 (1) and Epicryptophycin-1 (54). To a cooled (−30 °C) solution of cryptophycin-3 (**3**, 30.0 mg, 0.0486 mmol) in CH_2Cl_2 (1.62 mL) was added a solution of dimethyldioxirane in acetone (1.44 mL, 0.06 M, 0.0864 mmol) at −30 °C. The mixture was stirred at −30 °C for 6 h, and an additional 1.44 mL (0.06 M, 0.0864 mmol) of dimethyldioxi-

rane−acetone solution was added. The mixture was stirred at −30 °C for a further 18 h and was allowed to warm to room temperature. The solvent was removed in vacuo, the residue (38 mg) was dissolved in CH_2Cl_2, and the mixture of **1** and **54** was separated by reversed-phase HPLC (YMC-Pack ODS-AQ, S-5 μm, 120 A, 250 × 10 mm i.d.; UV dectection at 254 nm, MeOH/H_2O = 75:25, flow rate 3.5 mL/min) to afford **1** (t_R = 17.72 min) and its epimeric epoxide **54** (t_R = 19.51 min) as separate solutions in MeOH−H_2O. Solvents were removed in vacuo to give pure **1** (17.5 mg, 0.0268 mmol, 55%) and **54** (6.0 mg, 0.00917 mmol, 19%) as colorless films. Data for cryptophycin-1 (**1**): R_f 0.38 (50% acetone in hexanes, PMA); $[\alpha]^{22}_D$ +31.5 (*c* 1.75, MeOH); $[\alpha]^{22}_D$ +24.5 (*c* 1.50, $CHCl_3$) (lit.[9] $[\alpha]^{22}_D$ +33.8 (*c* 1.83, MeOH)); IR (film) 3409 (br), 3282 (br), 2959, 2925, 1748, 1728, 1679, 1504, 1176, 1069, 756 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.36 (m, 3H), 7.23 (m, 2H), 7.21 (dd, 1H, J = 2.1, 8.7 Hz), 7.05 (dd, 1H, J = 2.1, 8.4 Hz), 6.97 (br, 1H), 6.82 (d, 1H, J = 8.5 Hz), 6.68 (ddd, 1H, J = 5.4, 9.6, 15.1 Hz), 5.73 (d, 1H, J = 12.0 Hz), 5.70 (d, 1H, J = 4.6 Hz), 5.14 (m, 1H), 4.80 (m, 2H), 3.86 (s, 3H), 3.68 (d, 1H, J = 1.9 Hz), 3.46 (m, 1H), 3.30 (m, 1H), 3.14 (dd, 1H, J = 5.5, 14.5 Hz), 3.02 (dd, 1H, J = 7.3, 14.5 Hz), 2.92 (dd, 1H, J = 1.9, 7.4 Hz), 2.70 (m, 1H), 2.40−2.58 (m, 2H), 1.56−1.82 (m, 3H), 1.37 (m, 1H), 1.22 (d, 3H, J = 7.3 Hz), 1.14 (d, 3H, J = 7.0 Hz), 0.86 (d, 3H, J = 6.9 Hz), 0.84 (d, 3H, J = 6.3 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 175.6, 170.9, 170.7, 165.3, 153.9, 141.0, 136.7, 129.7, 128.7, 128.5, 128.3, 125.6, 125.2, 122.4, 112.2, 76.1, 71.3, 63.0, 59.0, 56.1, 53.7, 41.0, 40.6, 39.4, 38.2, 36.7, 35.0, 24.5, 22.9, 21.3, 14.1, 13.5; HRMS (FAB, *m*/*z*) calcd for $C_{35}H_{44}N_2O_8{}^{35}Cl$ (M^+ + H) 655.2786, found 655.2786.

Data for epicryptophycin-1 (**54**): R_f 0.38 (50% acetone in hexanes, PMA); $[\alpha]^{22}_D$ +10.3 (*c* 0.60, $CHCl_3$); IR (film) 3409 (br), 3277 (br), 2964, 2925, 1748, 1733, 1666, 1504, 1469, 1264, 1181, 1070, 760 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.35 (m, 3H), 7.25 (m, 3H), 7.10 (dd, 1H, J = 2.2, 8.5 Hz), 6.97 (br, 1H), 6.84 (d, 1H, J = 8.3 Hz), 6.70 (ddd, 1H, J = 5.5, 9.6, 15.2 Hz), 5.82 (d, 1H, J = 15.4 Hz), 5.70 (d, 1H, J = 8.4 Hz), 5.15 (m, 1H), 4.92 (m, 1H), 4.82 (m, 1H), 3.88 (s, 3H), 3.60 (d, 1H, J = 1.9 Hz), 3.50 (m, 1H), 3.32 (m, 1H), 3.16 (dd, 1H, J = 5.5, 14.4 Hz), 3.05 (dd, 1H, J = 7.3, 14.4 Hz), 2.90 (m, 1H), 2.40−2.78 (m, 3H), 1.76 (m, 3H), 1.50 (m, 1H), 1.24 (d, 3H, J = 7.4 Hz), 1.05 (d, 3H, J = 7.0 Hz), 0.91 (d, 3H, J = 6.5 Hz), 0.88 (d, 3H, J = 6.3 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 175.6, 171.0, 170.8, 165.4, 154.0, 141.4, 137.1, 131.0, 129.8, 128.6, 128.4, 128.3, 125.4, 125.2, 122.4, 112.2, 77.2, 71.5, 63.2, 56.3, 56.1, 53.6, 41.1, 40.0, 39.3, 38.3, 36.7, 35.1, 24.7, 23.1, 21.3, 14.1, 13.5; HRMS (FAB, *m*/*z*) calcd for $C_{35}H_{44}N_2O_8{}^{35}Cl$ (M^+ + H) 655.2786, found 655.2787.

Benzyl (2*S*)-2-[(2*R*)-3-[(2*R*)-2-*tert*-Butoxycarbonylamino-3-(4-methoxyphenyl)propionylamino]-2-methylpropionyloxy]-4-methylpentanoate (44). To a solution of **42** (133 mg, 0.327 mmol) in CH_2Cl_2 (1.63 mL) at 0 °C was added CF_3CO_2H (1.63 mL), and the mixture was stirred at 0 °C for 1 h. The solvent was removed in vacuo, and the residual crude **43** (172 mg) was dried by azeotropic removal of H_2O with toluene. To a cooled (0 °C) solution of crude **43** (172 mg, 0.327 mmol) and *N*-Boc-*O*-methyl-D-3-chlorotyrosine (125.4 mg, 0.425 mmol) in THF (2.64 mL) and CH_2Cl_2 (0.66 mL) were added 1-hydroxybenzotriazole (HOBT, 44.2 mg, 0.327 mmol), Et_3N (79.4 mg, 0.110 mL, 0.785 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI, 81.5 mg, 0.425 mmol). The mixture was stirred at 0 °C for 0.5 h and then was allowed to warm to room temperature and was stirred for a further 18 h. The solvent was removed in vacuo, and the residue was taken up in Et_2O. The ethereal solution was washed with H_2O, and the organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash chromatography (silica gel, elution with 50% Et_2O in hexanes) to give 178.3 mg (0.305 mmol, 93%) of **44** as a colorless oil: R_f 0.42 (50% EtOAc in hexanes, PMA); $[\alpha]^{22}_D$ −36.2 (*c* 1.21, $CHCl_3$); IR (film) 3302 (br), 2959, 2934, 1738, 1660, 1513, 1247, 1175 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.32 (m, 5H), 7.05 (d, 2H, J = 8.5 Hz), 6.82 (br, 1H), 6.75 (d, 2H, J = 8.4 Hz), 5.12 (m, 4H), 4.30 (m, 1H), 3.70 (s, 3H), 3.54 (m, 1H), 3.17 (ddd, 1H, J = 5.1, 8.8, 13.8 Hz), 2.96 (m, 2H), 2.70 (m, 1H), 1.60−1.77 (m, 3H), 1.36 (s, 9H), 1.11 (d, 3H, J = 7.0 Hz), 0.89 (d, 3H, J = 6.4 Hz), 0.87 (d, 3H, J = 6.3 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.9, 171.5, 170.9, 158.4, 155.1, 134.9, 130.2, 128.6, 128.5, 128.5, 128.2, 113.8, 79.5, 70.7, 67.2, 55.8, 55.0, 41.6, 40.0, 39.3, 38.0, 28.2, 24.6, 22.8, 21.4, 14.5; HRMS (CI, *m*/*z*) calcd for $C_{32}H_{45}N_2O_8$ (M^+ + H) 585.3176, found 585.3166.

***tert*-Butyl (5*S*,6*R*)-5-[(2*S*)-2-[(2*R*)-3-[(2*R*)-2-*tert*-Butoxycarbonylamino-3-(4-methoxyphe-nyl)-propionylamino]-2-methylpropionyloxy]-4-methylpentanoyloxy]-6-methyl-8-henylocta-2-(*E*),7(*E*)-dienoate (50).** To a solution of **44** (178.3 mg, 0.305 mmol) in EtOAc (4.36 mL) was added $Pd(OH)_2$ (20% on carbon, 21.4 mg, 0.0305 mmol), and the mixture was stirred vigorously at room temperature under a H_2 atmosphere for 2 h. The solution was filtered, and the filtrate was concentrated in vacuo. The resulting crude acid **45** (162.4 mg) was dried by azeotropic removal of H_2O with toluene and was used for the next reaction without further purification. To a solution of **19** (30.2 mg, 0.100 mmol) and crude **45** (80.0 mg, 0.150 mmol) in CH_2Cl_2 (0.83 mL) at room temperature was added 4-(dimethylamino)pyridine (DMAP, 18.3 mg, 0.150 mmol) followed slowly by 1,3-diisopropylcarbodiimide (DIC, 19.0 mg, 0.024 mL, 0.150 mmol). The mixture was stirred at room temperature for 18 h, and the solvent was removed in vacuo. The residue was purified by flash chromatography (silica gel, gradient elution with 25% and 50% Et_2O in hexanes) to give 65.0 mg (0.0837 mmol, 84%) of **50** as a colorless oil: R_f 0.55 (50% EtOAc in hexanes, PMA); $[\alpha]^{22}_D$ −5.4 (*c* 1.33, $CHCl_3$); IR (film) 3332 (br), 2978, 2937, 1740, 1718, 1658, 1510, 1247, 1169 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.18−7.30 (m, 5H), 7.14 (d, 2H, J = 8.4 Hz), 6.86 (br, 1H), 6.80 (d, 2H, J = 8.6 Hz), 6.40 (d, 1H, J = 15.8 Hz), 6.00 (dd, 1H, J = 8.7, 15.9 Hz), 5.82 (d, 1H, J = 15.7 Hz), 5.57 (m, 1H), 5.06 (m, 1H), 4.96 (dd, 1H, J = 3.8, 9.7 Hz), 3.74 (s, 3H), 3.60 (m, 1H), 3.15 (m, 2H), 2.92 (m, 1H), 2.40−2.68 (m, 4H), 1.50−1.70 (m, 3H), 1.48 (s, 9H), 1.34 (s, 9H), 1.14 (d, 3H, J = 8.9 Hz), 1.12 (d, 3H, J = 6.9 Hz), 0.84 (d, 3H, J = 6.3 Hz), 0.79 (d, 3H, J = 6.3 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.6, 171.7, 170.8, 165.6, 158.3, 155.5, 141.6, 136.7, 131.8, 130.2, 129.9, 129.3, 128.5, 127.4, 126.1, 113.8, 106.0, 80.3, 79.4, 76.6, 70.6, 56.1, 55.1, 41.9, 40.8, 40.5, 39.5, 37.7, 34.7, 29.6, 28.2, 28.1, 24.6, 22.8, 21.3, 16.9, 14.5; HRMS (FAB, *m*/*z*) calcd for $C_{44}H_{63}N_2O_{10}$ (M^+ + H) 779.4482, found 779.4494.

Cryptophycin 4 (4). To a solution of **50** (65.0 mg, 0.0837 mmol) in CH_2Cl_2 (1.19 mL) at 0 °C was slowly added CF_3CO_2H (4.78 mL), and the mixture was allowed to warm to room temperature and was stirred for 2 h. The solvent was removed in vacuo, and the residue (81.0 mg) was dried by azeotropic removal of H_2O with toluene. To a cooled (0 °C) solution of the crude amine−TFA salt (81.0 mg, 0.0837 mmol) in dry DMF (10.5 mL) were added $NaHCO_3$ (42.3 mg, 0.504 mmol) and diphenyl phosphorazidate (DPPA, 34.5 mg, 0.0270 mL, 0.126 mmol), and the mixture was stirred at 0 °C for 72 h. The reaction was quenched by addition of H_2O, and the aqueous layer was extracted with EtOAc, CH_2Cl_2, and EtOAc again. The combined organic extract was washed with H_2O, dried ($MgSO_4$), filtered, and concentrated in vacuo, and the residue was purified by flash chromatography (silica gel, gradient elution with 50% EtOAc in hexanes, 17% and 25% acetone in hexanes) to give 30.6 mg (0.0507 mmol, 61%) of cryptophycin-4 **(4)** as a colorless oil: R_f 0.33 (50% acetone in hexanes, PMA); $[\alpha]^{22}_D$ +29.1 (*c* 2.1, $CHCl_3$) (lit.[9] $[\alpha]^{22}_D$ +22.8 (*c* 0.2, $CHCl_3$)); IR (film) 3414 (br), 3287 (br), 2957, 2930, 1745, 1726, 1655, 1513, 1247, 1177, 751 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.18−7.34 (m, 5H), 7.11 (d, 2H, J = 8.6 Hz), 7.08 (m, 1H), 6.80 (d, 2H, J = 8.5 Hz), 6.71 (ddd, 1H, J = 5.8, 10.8, 15.8 Hz), 6.40 (d, 1H, J = 15.8 Hz), 6.02 (dd, 1H, J = 8.8, 15.8 Hz), 5.75 (d, 1H, J = 10.7 Hz), 5.71 (d, 1H, J = 3.4 Hz), 5.03 (m, 1H), 4.85 (dd, 1H, J = 3.4, 9.7 Hz), 4.78 (m, 1H), 3.77 (s, 3H), 3.39 (m, 2H), 3.14 (dd, 1H, J = 5.5, 14.4 Hz), 3.06 (dd, 1H, J = 7.2, 14.5 Hz), 2.68 (m, 1H), 2.52 (m, 2H), 2.35 (m, 1H), 1.64 (m, 2H), 1.45 (m, 1H), 1.22 (d, 3H, J = 7.2 Hz), 1.12 (d, 3H, J = 6.9 Hz), 0.75 (d, 3H, J = 6.4 Hz), 0.72 (d, 3H, J = 6.4 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 175.9, 171.2, 170.8, 165.3, 158.5, 141.5, 136.7, 131.7, 130.2, 128.6, 128.5, 127.5, 126.1, 125.0,

114.1, 77.2, 71.5, 55.2, 53.9, 42.2, 40.7, 39.5, 38.1, 36.4, 35.3, 24.4, 22.6, 21.2, 17.3, 14.1; HRMS (FAB,*m*/*z*) calcd for $C_{35}H_{45}N_2O_7$ ($M^+ + H$) 605.3227, found 605.3222.

Benzyl (2*S*)-2-[3-[(2*R*)-2-*tert*-Butoxycarbonylamino-3-(3-chloro-4-methoxyphenyl)propionylamino]propionyloxy]-4-methylpentanoate (36). A solution of **30** (129 mg, 0.327 mmol) in CH_2Cl_2 (1.63 mL) at 0 °C was added CF_3CO_2H (1.63 mL), and the mixture was stirred at 0 °C for 1 h. The solvent was removed in vacuo, the residue (148 mg) was dried by azeotropic removal of H_2O with toluene, and the resultant crude **31** was subjected to the next reaction without further purification.

To a cooled (0 °C) solution of crude **31** (148 mg, 0.327 mmol) and *N*-Boc-*O*-methyl-D-3-chlorotyrosine (61.5 mg, 0.160 mmol) in THF (1.28 mL) and CH_2Cl_2 (0.32 mL) were added 1-hydroxybenzotriazole (HOBT, 32.4 mg, 0.240 mmol), Et_3N (40.5 mg, 0.560 mL, 0.400 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI, 61.4 mg, 0.320 mmol). The mixture was stirred at 0 °C for 0.5 h and then was allowed to warm to room temperature and was stirred for a further 18 h. The solvent was removed in vacuo, and the residue was taken up in Et_2O. The ethereal solution was washed with H_2O, and the organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash chromatography (silica gel, gradient elution with 33% and 50% Et_2O in hexanes) to give 92.7 mg (0.153 mmol, 96%) of **36** as a colorless oil: R_f 0.41 (50% EtOAc in hexanes, PMA); $[\alpha]^{22}_D$ −21.9 (*c* 1.32, $CHCl_3$); IR (film) 3316 (br), 2964, 2930, 1743, 1659, 1504, 1257, 1170 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.33 (m, 5H), 7.18 (d, 1H, J = 2.0 Hz), 7.02 (dd, 1H, J = 2.0, 8.4 Hz), 6.81 (br. 1H), 6.80 (d, 1H, J = 8.4 Hz), 5.15 (m, 4H), 4.30 (m, 1H), 3.82 (s, 3H), 3.58 (m, 1H), 3.49 (m, 1H), 3.02 (dd, 1H, J = 6.2, 12.9 Hz), 2.90 (m, 1H), 2.54 (t, 2H, J = 6.4 Hz), 1.60−1.80 (m, 3H), 1.37 (s, 9H), 0.90 (d, 3H, J = 5.8 Hz), 0.88 (d, 3H, J = 5.8 Hz), 0.88 (d, 3H, J = 5.9 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.3, 171.0, 170.9, 155.1, 153.7, 134.9, 131.0, 129.8, 128.6, 128.4, 128.1, 122.0, 112.0, 79.8, 71.0, 67.3, 56.0, 55.5, 39.3, 37.6, 35.0, 34.1, 28.1, 24.5, 22.8, 21.4; HRMS (CI, *m*/*z*) calcd for $C_{31}H_{42}N_2O_8{}^{35}Cl$ ($M^+ + H$) 605.2629, found 605.2616.

***tert*-Butyl (5*S*,6*R*)-5-[(2*S*)-2-[3-[(2*R*)-2-(*tert*-Butoxycarbonylamino)-3-(3-chloro-4-methoxyphenyl)propionylamino]propionyloxy]-4-methylpentanoyloxy]-6-methyl-8-phenylocta-2(*E*),-7(*E*)-dienoate (49).** To a solution of **36** (85.7 mg, 0.142 mmol) in EtOAc (2.0 mL) was added $Pd(OH)_2$ (20% on carbon, 10.0 mg, 0.0142 mmol), and the mixture was stirred vigorously at room temperature under a H_2 atmosphere for 2 h. The mixture was filtered, and the filtrate was concentrated in vacuo. The crude acid **37** (78.0 mg) was dried by azeotropic removal of H_2O with toluene and was subjected to the next reaction without further purification.

To a solution of **19** (31.0 mg, 0.103 mmol) and crude **37** (78.0 mg, 0.142 mmol) in CH_2Cl_2 (0.86 mL) at room temperature was added 4-(dimethylamino)pyridine (DMAP, 19.0 mg, 0.155 mmol), followed slowly by 1,3-diisopropylcarbodiimide (DIC, 19.5 mg, 0.024 mL, 0.155 mmol). The mixture was stirred at room temperature for 18 h, and the solvent was removed in vacuo. The residue was purified by flash chromatography (silica gel, gradient elution with 20% and 50% Et_2O in hexanes) to give 69.5 mg (0.0872 mmol, 85%) of **49** as a colorless oil: R_f 0.49 (50% EtOAc in hexanes, PMA); $[\alpha]^{22}_D$ +1.66 (*c* 1.39, $CHCl_3$); IR (film) 3350, 29656, 2931, 1741, 1713, 1658, 1504, 1257, 1168 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.18−7.32 (m, 6H), 7.07 (dd, 1H, J = 2.1, 8.3 Hz), 6.96 (br, 1H), 6.83 (d, 1H, J = 8.5 Hz), 6.81 (m, 1H), 6.40 (d, 1H, J = 15.8 Hz), 6.00 (dd, 1H, J = 8.7, 15.9 Hz), 5.83 (d, 1H, J = 15.6 Hz), 5.55 (m, 1H), 5.05 (m, 1H), 4.95 (dd, 1H, J = 3.9, 9.9 Hz), 4.36 (m, 1H), 3.83 (s, 3H), 3.52 (m, 2H), 3.15 (dd, 1H, J = 5.2, 14.0 Hz), 2.88 (m, 1H), 2.40−2.53 (m, 5H), 1.63 (m, 3H), 1.47 (s, 9H), 1.35 (s, 9H), 1.10 (d, 3H, J = 6.7 Hz), 0.82 (d, 3H, J = 6.4 Hz), 0.76 (d, 3H, J = 6.4 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.3, 170.8, 165.8, 155.4, 141.8, 136.7, 131.7, 131.1, 130.5, 130.0, 128.5, 127.4, 126.1, 121.9, 112.0, 80.4, 79.5, 76.4, 71.2, 56.0, 55.6, 41.0, 39.5, 37.4, 35.1, 34.8, 34.2, 28.2, 28.1, 24.5, 22.7, 21.2, 16.9; HRMS (FAB, *m*/*z*) calcd for $C_{43}H_{60}N_2O_{10}{}^{35}Cl$ ($M^+ + H$) 799.3937, found 799.3947.

Cryptophycin-29 (6). To a solution of **49** (69.5 mg, 0.0872 mmol) in CH_2Cl_2 (1.24 mL) at 0 °C was slowly added CF_3CO_2H (4.98 mL), and the mixture was allowed to warm to room temperature and was stirred for a further 2 h. The solvent was removed in vacuo, and the residue (86.9 mg) was dried by azeotropic removal of H_2O with toluene and used for the next reaction without further purification.

To a cooled (0 °C) solution of the crude amine−TFA salt (86.9 mg, 0.0872 mmol) in dry DMF (10.9 mL) were added $NaHCO_3$ (44.0 mg, 0.523 mmol) and diphenyl phosphorazidate (DPPA, 36.0 mg, 0.028 mL, 0.131 mmol), and the mixture was stirred at 0 °C for 72 h. The reaction was quenched by addition of H_2O, and the aqueous layer was extracted with EtOAc, CH_2Cl_2, and EtOAc again. The combined organic extract was washed with H_2O, dried ($MgSO_4$), filtered, and concentrated in vacuo, and the residue was purified by flash chromatography (silica gel, gradient elution with 20% and 33% acetone in hexanes) to give 31.6 mg (0.0506 mmol, 58% for two steps) of cryptophycin-29 **(6)** as a colorless oil: R_f 0.28 (50% acetone in hexanes, PMA); $[\alpha]^{22}_D$ +32.5 (*c* 1.17, $CHCl_3$) (li.[3] $[\alpha]^{22}_D$ +22.2 (*c* 1.13, $CHCl_3$)); IR (film) 3409, 3277 (br), 2958, 2928, 1742, 1673, 1503, 1258, 1173, 750 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.18−7.32 (m, 6H), 7.06 (dd, 1H, J = 2.1, 8.5 Hz), 6.99 (br, 1H), 6.82 (d, 1H, J = 8.5 Hz), 6.69 (ddd, 1H, J = 5.0, 10.2, 15.2 Hz), 6.40 (d, 1H, J = 15.8 Hz), 6.03 (d, 1H, J = 8.8 Hz), 5.98 (d, 1H, J = 8.7 Hz), 5.78 (d, 1H, J = 15.8 Hz), 5.03 (m, 1H), 4.89 (dd, 1H, J = 3.5, 9.8 Hz), 4.74 (m, 1H), 3.85 (s, 3H), 3.49 (m, 2H), 3.15 (dd, 1H, J = 5.8, 14.4 Hz), 2.97 (dd, 1H, J = 7.7, 14.4 Hz), 2.34−2.60 (m, 4H), 1.55−1.65 (m, 3H), 1.33 (m, 1H), 1.13 (d, 3H, J = 6.8 Hz), 0.74 (d, 3H, J = 6.3 Hz), 0.70 (d, 3H, J = 6.4 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.6, 170.8, 170.6, 165.7, 153.8, 141.4, 136.7, 131.8, 130.9, 130.2, 130.0, 128.6, 128.4, 127.5, 126.1, 125.2, 122.3, 112.2, 77.0, 71.4, 56.1, 54.0, 42.3, 39.7, 36.4, 34.9, 34.4, 32.4, 24.3, 22.6, 21.2, 17.2; HRMS (FAB, *m*/*z*) calcd for $C_{34}H_{42}N_2O_7{}^{35}Cl$ ($M^+ + H$) 625.2681, found 625.2675.

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Supporting Information Available: NMR spectra of synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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