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Enantioselective Synthesis of (+)-Cryptophycin 52 (LY355703), a Potent Antimitotic Antitumor Agent

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Abstract: A highly enantioselective and convergent synthesis of cryptophycin 52 (**2**), an exceedingly potent cytotoxic agent, is described. Cryptophycin 52, a synthetic variant of the cryptophycin family, is currently undergoing clinical trials. The synthesis is convergent and involves assembly of three fragments, phenyl hexenal **3**, D-tyrosine phosphonate **4**, and protected β-amino acid derivative **5**. The synthesis of fragment **3** involves an efficient and stereocontrolled construction of both stereogenic centers at C-3 and C-4 by cleavage of a substituted tetrahydrofuran ring via an acyloxycarbenium ion intermediate. Both of these stereogenic centers were derived from optically active 4-phenylbutyrolactone, synthesized enantioselectively by Corey−Bakshi−Shibata reduction.

Cryptophycins are a family of macrocyclic depsipeptides isolated from terrestrial blue-green algae *Nostoc* sp. GSV 224 that have shown exceedingly potent antitumor properties.[1] Cryptophycin A displayed potent cytotoxicity against KB and LoVo cell lines with IC_{50} values of 3 and 5 pg/mL, respectively,[2] and has been shown to be very effective against mammary, colon, and pancreatic adenocarcinomas in mouse xenograft models.[3] Cryptophycin 52, a synthetic analogue, is currently undergoing phase II clinical trials.[4] This derivative has shown exceptional in vivo potency and tumor-selective cytotoxicity. Furthermore, it is effective against drug-sensitive and drug-resistant tumor cells and is metabolically more stable than cryptophycin A.[5] Cryptophycin 52 stabilizes microtubule dynamics and appears to display a mechanism of action consistent with mitotic arrest.[6] Recent studies also indicated that cryptophycin 52 promotes hyperphosphorylation of Bcl_2 and may be involved in a second pathway to apoptosis, similar to but considerably more potent than paclitaxel.[7] Thus, it is not surprising that the significant clinical potential of cryptophycins has generated enormous interest in their synthesis, structural modification, and biological studies. Several total syntheses and synthetic approaches to cryptophycins have been reported.[8] In this context, a number of interesting methodologies, particularly for the synthesis of the octadienamide fragment of desoxycryptophycins, have been developed.[9] We recently reported the synthesis of cryptophycin B utilizing an ester-derived titanium enolate aldol reaction as the key step.[8b] Subsequently, we explored a nonaldol strategy for the preparation of the key octadienamide fragment. Herein we describe a highly enantioselective and convergent synthesis of cryptophycin 52 utilizing optically active phenylbutyrolactone. Both stereogenic centers of the octadienamide unit were created on the basis of the chirality of 4-phenylbutyrolactone, and the latter was prepared enantioselectively by CBS reduction.

As depicted in Figure 1, our synthetic strategy for cryptophycin 52 is convergent and involves assembly of three fragments, phenyl hexenal **3**, D-tyrosine phosphonate **4**, and protected β-amino acid derivative **5**. A Horner−Emmons olefination between aldehyde **3** and phosphonate **4** would generate the key tyrosine octadienamide subunit. Esterification with acid **5** would afford the corresponding protected acyclic precursor for cryptophycin 52. Removal of the appropriate protecting groups followed by cycloamidation of the resulting amino acid would construct the 16-membered macrocyclic ring. We planned to incorporate the sensitive epoxide functionality at the final stage of the synthesis. Both stereogenic centers in fragment **3** are planned to be accessed on the basis of the chirality of optically active 4-phenylbutyrolactone **8,** which can be prepared on a multigram scale utilizing an enantioselective CBS reduction as the key step. To this end, we developed an efficient, scalable, and highly stereocontrolled synthesis of **3** and, consequently, the corresponding octadienamide fragment.

As shown in Scheme 1, enantioselective CBS reduction of readily available[10] ketoester **6** with 8 mol % oxazaborolidine **7** afforded the corresponding (*S*)-alcohol as described by Corey.[11] The resulting γ-hydroxyester was lactonized by heating with a catalytic amount of acetic acid in toluene to furnish the key lactone **8** in 84% yield

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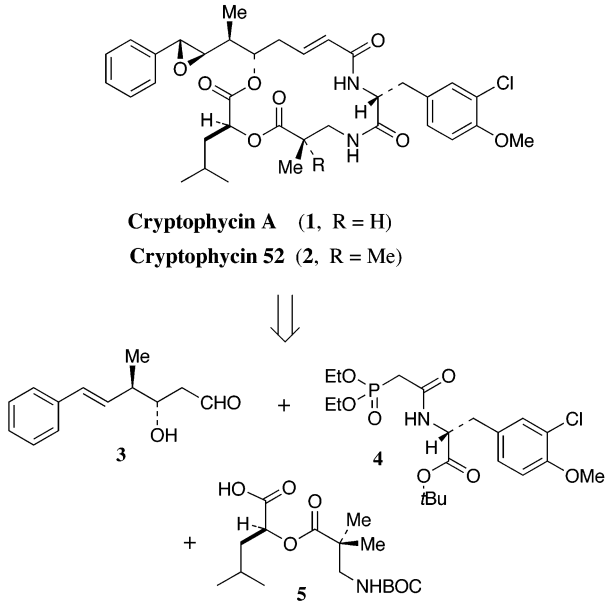
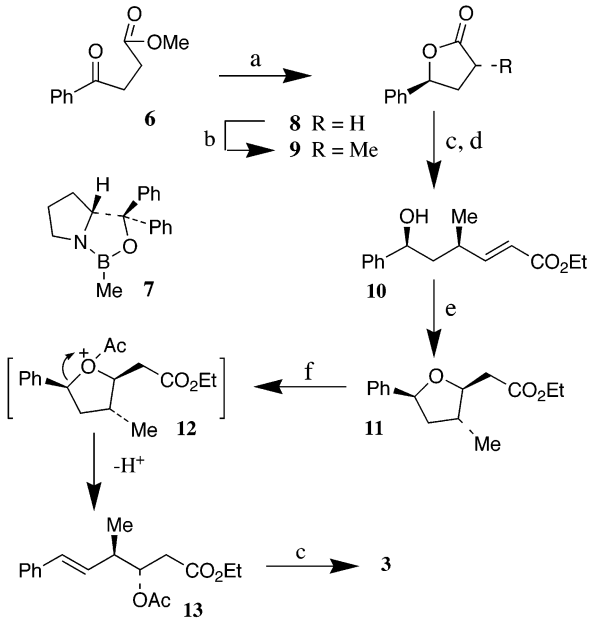


FIGURE 1. Retrosynthetic analysis of cryptophycin 52.

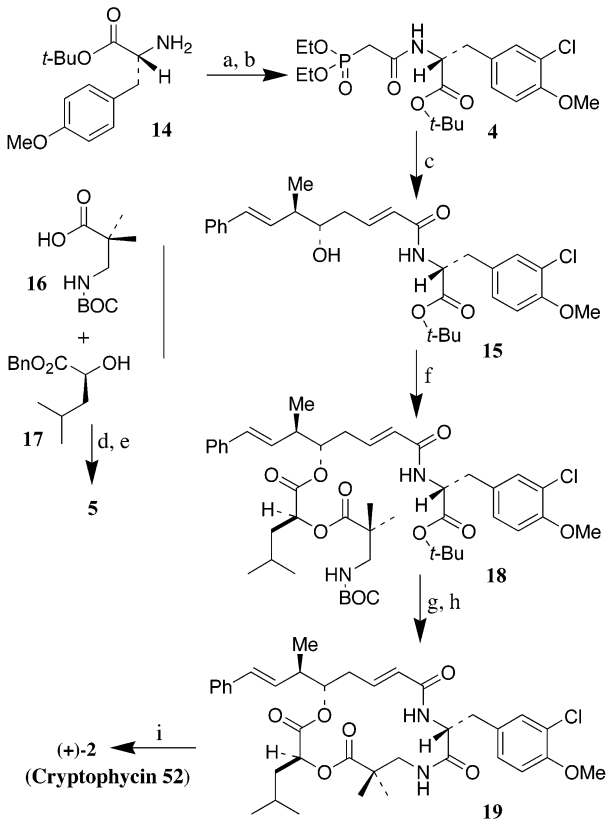
SCHEME 1[a]



[a] (a) (*R*)-Oxazaborolidine **7** (8 mol %), BH_3·THF, then AcOH, toluene, reflux; (b) LiHMDS, MeI, −78 °C; (c) DIBAL-H, CH_2Cl_2, −78 °C; (d) $Ph_3P{=}CHCO_2Et$, CH_2Cl_2, 40 °C; (e) KHMDS, THF, −78 °C; (f) Ac_2O, $ZnCl_2$ (catalytic, 6 mol %), 120 °C.

and optical purity >97% ee.[12] For introduction of the methyl substiutent at C-6, alkylation of **8** was carried out with LiHMDS and MeI in THF at −78 °C to provide alkylated lactone **9** as the major diastereomer along with about 3% *cis*-alkylation product, which was separated by silica gel chromatography providing **9** in 75% yield. DIBAL reduction of **9** followed by Wittig olefination of the resulting lactol furnished α,β-unsaturated ester **10** in 89% yield with *E*/*Z* selectivity >55:1. Treatment of **10** with KHMDS in THF at −78 °C afforded tetrahydrofuran derivative **11** diastereoselectively in 90% yield. A diastereomeric ratio of 22:1 was determined on the basis of ^{1}H NMR integration of the benzylic proton. The mixture was inseparable by silica gel chromatography; therefore, it was used for the subsequent reaction. With the installation of the corresponding C-3 and C-4 stereogenic centers of **3**, our synthetic strategy was to unravel the cyclic stereochemistry of **11** to acyclic intermediate **13** with the appropriate styryl olefin geometry. It is known that 2-phenyltetrahydrofuran can be selectively cleaved by acetic anhydride in the presence of a catalytic amount of acid or metal halides to form 4-acetoxy-1-phenylbut-1-ene.[13] We therefore envisioned an acyloxycarbenium ion mediated ring opening of **11** that would provide **13** through formation of a stable benzylic carbonium ion and subsequent loss of a proton. Indeed, reaction of **11** in acetic anhydride in the presence of a catalytic amount of $ZnCl_2$ (6 mol %) at 120 °C for 8 h provided **13** in 91% yield as a single isomer by ^{1}H and

SCHEME 2[a]



[a] (a) $(EtO)_2P(O)CH_2CO_2H$, DCC, THF, 23 °C, 1 h; (b) KCl, Oxone, aq. MeCN, 23 °C; (c) NaH, THF, then **3**, 0 to 23 °C; (d) EDCI, DMAP, CH_2Cl_2; (e) H_2, 10% Pd−C; (f) **5**, 2,4,6-$Cl_3C_6H_2COCl$, Et_3N, then **15**, 23 °C; (g) CF_3CO_2H, 23 °C, 2 h; (h) FDPP, DMF, iPr_2NEt, 23 °C; (i) *m*-CPBA, CH_2Cl_2, 0 to 23 °C, 12 h (70%, 2:1 mixture).

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^{13}C NMR analysis. Subsequently, DIBAL reduction provided the requisite aldehyde for Horner−Emmons reaction.

The synthesis of phosphonate derivative **4** was carried out in two steps as shown in Scheme 2. Diethoxyphosphenyl acetic acid[14] was coupled with tyrosine derivative **14**[8b] in the presence of DCC to provide the corresponding amide in 96% yield. Electrophilic chlorination[15] with KCl and oxone provided chlorotyrosine derivative **4** in 75% yield after silica gel chromatography. This method mildly chlorinates the D-tyrosine derivative in the presence of the acid-sensitive *tert*-butyl ester. Our initial synthetic plan for **4** was to carry out electrophilic chlorination of the corresponding Cbz-tyrosine derivative of **14**, remove the Cbz group, and then couple with diethoxyphosphinyl acetic acid. Although the above chlorination reaction conditions provided the corresponding *meta*-chlorotyrosine in excellent yield (70%), our attempt to remove the Cbz group by a catalytic hydrogenation under a variety of conditions resulted in a substantial dechlorination (25−40%). Horner−Emmons reaction of **4** and aldehyde **3** furnished the α,β-unsaturated amide derivative **15** in 52% yield over two steps (from **13**). The synthesis of β-amino acid derivative **5** was carried out by esterification of known *N*-Boc-3-amino-2,2-dimethylpropionic acid **16**[16] and benzyl (*S*)-2-hydroxyisocaproate **17**[8b] with EDC and DMAP in CH_2Cl_2. Catalytic hydrogenation of the resulting diester over 10% Pd/C in ethyl acetate under a hydrogen-filled balloon for 1.5 h furnished acid **5** in quantitative yield. Acid **5** was subjected to esterification by reaction with 2,4,6-trichlorobenzoyl chloride, triethylamine, and alcohol **15** in the presence of DMAP under Yamaguchi conditions[17] to afford diester **18** in 77% yield after silica gel chromatography. Diester **18** was converted to desoxycryptophycin 52 in two steps involving the removal of both the *tert*-butyl ester and Boc-protecting group by exposure of **18** to trifluoroacetic acid and subjection of the resulting amino acid to cycloamidation with pentafluorophenyl diphenylphosphinate (FDPP) and *i*Pr$_2$NEt as described by Tius et al.[8g] to provide **19** ($[\alpha]^{23}_D$ +26.2, *c* 0.5, $CHCl_3$) in 61% yield over two steps. To complete the synthesis of cryptophycin 52, epoxidation of **19** was carried out with *m*-CPBA to furnish cryptophycin 52 and its diastereomer as a 2:1 mixture in 70% yield. The epoxide mixture was separated by reverse phase HPLC (eluent, 45% aqueous CH_3CN) to provide synthetic cryptophycin 52 (**2**, $[\alpha]^{23}_D$ +20, *c* 0.08, $CHCl_3$; lit.[16] $[\alpha]_D$ 19.9, *c* 0.5, $CHCl_3$). Spectral data (400 MHz ^{1}H and ^{13}C NMR) of our synthetic cryptophycin 52 are in full agreement with the reported values for cryptophycin 52.[16]

In conclusion, an efficient synthesis of cryptophycin 52 was achieved. The synthesis of the octadienamide fragment highlighted efficient construction of two stereogenic centers by selective cleavage of the tetrahydrofuran ring derived from optically active 4-phenylbutyrolactone. Selective chlorination of the tyrosine aromatic ring in the presence of multiple functionalities is also noteworthy. The present synthetic route is scalable and easily amenable to the synthesis of other members of the cryptophycin family.

Experimental Section

General. ^{1}H and ^{13}C NMR spectra were obtained in $CDCl_3$ at 400 MHz for ^{1}H and 100 MHz for ^{13}C. Chemical shifts are reported in ppm and coupling constants (J) are reported in Hertz. Optical rotations were measured using a polarimeter using a sodium lamp (589 nm) in chloroform unless otherwise stated. Infrared spectra were measured in chloroform as thin films using sodium chloride plates. Thin-layer chromatography (TLC) was performed on silica gel 60-F-254 plates. Mass spectra were recorded on a mass spectrometer as the value *m*/*z*. Flash chromatography was performed using 230−400 mesh silica gel. Tetrahydrofuran was distilled from sodium/benzophenone, and benzene, methylene chloride, *N*,*N*-dimethylformamide, and toluene were distilled from CaH_2 under N_2.

Ethyl (3*S*,4*R*)-3-Acetoxy-4-methyl-6-phenyl-hexan-(5*E*)-oate (13). A solution of 1.84 g (7.43 mmol) of cyclic ether **11** and 60 mg (0.44 mmol) of $ZnCl_2$ in 20 mL of Ac_2O was heated at 120 °C for 8.5 h. Ethyl acetate (80 mL) was added, and the solution was washed 8 × 50 mL with 5% $NaHCO_3$ solution. The organic layer was then dried over Na_2SO_4, filtered, and concentrated. Flash silica gel chromatography (6% to 10% ethyl acetate/hexanes) provided product **13** as a yellow oil in 91% yield (1.97 g). $[\alpha]^{23}_D$ + 20.8 (*c* 0.49, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.2−7.36 (m, 5H), 6.42 (d, 1H, *J* = 15.9), 6.1 (dd, 1H, *J* = 8.3, 15.9), 5.33 (td, 1H, *J* = 5.2, 7.4), 4.11 (m, 2H), 2.66 (m, 1H), 2.56 (m, 2H), 2.04 (s, 3H), 1.23 (t, 3H, *J* = 7.1), 1.12 (d, 3H, *J* = 6.9); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 170, 137, 131.5, 130.1, 128.5, 127.3, 126.1, 73.0, 60.6, 40.9, 36.9, 20.9, 16.0, 14.1; IR (neat) 1741 cm^{-1}; MS (ESI, *m*/*z*) 313.1 (M + Na)$^+$; HRMS (ESI, *m*/*z*) calcd for $C_{17}H_{22}O_4Na$ (M + Na)$^+$ 313.1416, found 313.1418.

3-(3-Chloro-4-methoxy-phenyl)-(2*R*)-2-((5*S*,6*R*)-5-hydroxy-6-methyl-8-phenyl-octa-2(*E*),7(*E*)-dienoylamino)-propionic Acid *tert*-Butyl Ester (15). To a stirring solution of 117 mg (0.41 mmol) of alkene **13** in 10 mL of CH_2Cl_2 at −78 °C was added 1 mL of DIBAL-H (1 M in hexanes) followed by 0.4 mL over a period of about 30 min, and the reaction was monitored to ensure all starting material was consumed. After 40 min, 7 mL of 2-propanol was added, the dry ice−acetone bath was removed, and the reaction was allowed to warm to 23 °C. After 30 min an aqueous solution of potassium sodium tartrate tetrahydrate (10 g in 60 mL of water) was added, and the mixture was stirred at 23 °C for 1 h. The layers were separated, and the organic layer was washed with 5 mL of brine and dried over Na_2SO_4. The solution was filtered and concentrated with dry benzene, and the crude aldehyde **3** was used in the next reaction without further purification.

To a stirring solution of 190 mg (0.41 mmol) of phosphonamide **4** in 10 mL of THF at 0 °C was added 40 mg (1 mmol) of NaH (60% dispersion in mineral oil). After stirring for 1 h, the crude aldehyde **3** was added in 10 mL of THF, and the ice bath was removed. After 1.5 h, 4 mL of saturated NH_4Cl solution was added along with 8 mL of water. Ethyl acetate (20 mL) was added, and the layers were separated. The organic layer was washed with 6 mL of brine, dried over Na_2SO_4, filtered, and concentrated. Purification by flash silica gel chromatography gave the product **15** as a white solid (109 mg) in 52% yield. Mp 45−48 °C; $[\alpha]^{23}_D$ −48 (*c* 0.76, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, 2H *J* = 7.4), 7.30 (m, 2H), 7.22 (m, 1H), 7.15 (d, 1H, *J* = 2.1), 7.00 (dd, 1H, *J* = 2.1, 8.4), 6.90 (ddd, 1H, *J* = 7.4, 7.5, 14.9), 6.82 (d, 1H, *J* = 8.4), 6.45 (d, 1H, *J* = 15.9), 6.15 (dd, 1H, *J* = 8.7, 15.9), 6.11 (d, 1H, *J* = 7.5), 5.89 (d, 1H, *J* = 15.3), 4.79 (ddd, 1H, *J* = 4.4, 5.7, 7.5 Hz), 3.87 (s, 3H), 3.66 (ddd, 1H, *J* = 4.2, 5.4, 8.2 Hz), 3.05 (d, 2H, *J* = 5.7), 2.44 (m, 2H), 2.34 (m, 1H), 1.9 (s, 1H), 1.43 (s, 9H), 1.15 (d, 3H, *J* = 7.03); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 164.9, 153.9, 141.6, 137.0, 131.7, 131.2, 131.0, 129.2, 128.7, 128.5, 127.3, 126.1, 125.6, 122.0, 111.8,

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82.7, 73.7, 56.0, 53.5, 43.1, 37.2, 36.8, 27.9, 16.8; IR (neat) 3405, 1729, 1670, 1634, 1503, 1368, 1258 cm^{-1}; MS (ESI, *m*/*z*) 536.1 $(M + Na)^+$; HRMS (ESI, *m*/*z*) calcd for $C_{29}H_{36}NO_5NaCl$ $(M + Na)^+$ 536.2180, found 536.2200.

(2*S*)-2-[3′(*tert*-Butyloxycarbonyl)amino-2′,2′-dimethylpropanoyloxy]-4-methylpentanoic Acid (5). To a stirring solution of 143 mg (0.76 mmol) of BOC-protected amino acid **16** and 116 mg (0.52 mmol) of benzyl ester **17** in 12 mL of CH_2Cl_2 at 0 °C were added 148 mg (0.77 mmol) of EDCI and 95 mg (0.77 mmol) of DMAP. Stirring was continued at 23 °C for 17 h. After this period, 10 mL of water and 10 mL of CH_2Cl_2 were added. The layers were separated, and the organic layer was washed with 10% aqueous HCl, saturated $NaHCO_3$ solution, and brine. The solution was dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash silica gel chromatography (8% EtOAc/hexanes) to give 172 mg (78%) of ester product as a yellow oil. $[\alpha]^{23}_D$ −40.5 (*c* 0.64, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.36 (m, 5H), 5.41 (t, 1H, J = 6.3), 5.18 (dd, 2H, J = 12.2, 24), 5.09 (dd, 1H, J = 3.6, 9.8), 3.28 (m, 2H), 1.81 (m, 1H), 1.76−1.62 (m, 2H), 1.43 (s, 9H), 1.20 (s, 6H), 0.92 (dd, 6H, J = 6.3, 10.0); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.4, 170.8, 156.3, 135.0, 128.5, 128.4, 128.3, 78.9, 70.8, 67.1, 48.5, 43.9, 39.3, 28.3, 24.7, 23.0, 22.9, 22.2, 21.4; IR (neat) 3392, 1737, 1721, 1510 cm^{-1}.

A mixture of 778 mg (1.85 mmol) of the above ester and 81 mg of 10% Pd−C in 25 mL of ethyl acetate was stirred at 23 °C under a H_2 balloon for 1.5 h. The mixture was then filtered through Celite and concentrated. The crude product was subjected to flash silica gel chromatography (10% MeOH/CH_2Cl_2) to give the acid **5** in quantitative yield as a colorless oil. $[\alpha]^{23}_D$ −32.5 (*c* 0.55, MeOH); lit.[5] $[\alpha]^{23}_D$ −29.9 (*c* 1.1, MeOH); ^1H NMR (400 MHz, $CDCl_3$) δ 5.4 (m, 1H), 5.08 (dd, 1H, J = 3.4, 9.7), 3.28 (m, 2H), 1.7−1.9 (m, 3H), 1.42 (s, 9H), 1.22 (s, 3H), 1.20 (s, 3H), 0.97 (d, 3H, J = 6.3 Hz), 0.93 (d, 3H, J = 6.1); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.5, 175.5, 156.5, 79.1, 70.5, 48.5, 43.9, 39.4, 28.3, 24.7, 23.1, 22.1, 21.3; IR (neat) 3349, 1725, 1672, 1524, 1368 cm^{-1}; MS (ESI *m*/*z*) 354.2 $(M + Na)^+$.

(2*S*)-2-(3-*tert*-Butoxycarbonylamino-2,2-dimethyl-propionyloxy)-4-methyl-pentanoic Acid (1*S*,2*R*,2*E*)-1-{3-[1-*tert*-Butoxycarbonyl-(2*R*)-2-(3-chloro-4-methoxy-phenyl)-ethylcarbamoyl]-allyl}-2-methyl-4-phenyl-but-(3*E*)-enyl Ester (18). To a stirring solution of 117 mg (0.48 mmol) of 2,4,6-trichlorobenzoyl chloride in 5 mL of THF was added 139 mg (0.42 mmol) of acid **5** in 15 mL of THF followed by 78 μL (0.56 mmol) of Et_3N. The resulting mixture was continued to stir at 23 °C for 3.5 h and then concentrated.

To a stirring mixture of crude mixed anhydride in 5 mL of toluene was added 185 mg (0.36 mmol) of **15** in 8.5 mL of toluene, 56 μL (0.4 mmol) of Et_3N, and finally 5.5 mg (0.04 mmol) of DMAP. The mixture was stirred at 23 °C under N_2 for 30 min. After this period, 10 mL of 0.1 N HCl followed by 15 mL of ethyl acetate were added. The layers were separated, and the organic layer was washed with 5 mL of brine, dried over Na_2SO_4, and concentrated. The crude product was purified by flash silica gel chromatography (25% and 30% ethyl acetate/hexanes) to give 229 mg of **18** as a white solid in 77% yield. Mp 45−47 °C $[\alpha]^{23}_D$ −23 (*c* = 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.28−7.33 (m, 4H), 7.22 (m, 1H), 7.15 (d, 1H, J = 1.9), 7.02 (dd, 1H, J = 2, 8.5), 6.84 (d, 1H, J = 8.5), 6.82 (m, 1H), 6.42 (d, 1H, J = 15.7), 6.41 (d, 1H, J = 7.7), 6.02 (dd, 1H, J = 8.6, 15.7), 5.89 (d, 1H, J = 15.6), 5.44 (t, 1H, J = 6.5), 5.05 (td, 1H, J = 5.9, 6.0), 4.93 (dd, 1H, J = 3.6, 9.6), 4.78 (dd, 1H, J = 5.8, 13.3), 3.85 (s, 3H), 3.26 (d, 2H, J = 6.6), 3.04 (m, 2H), 2.63 (m, 1H), 2.54 (m, 2H), 1.64−1.76 (m, 2H), 1.55 (m, 1H), 1.43 (s, 9H), 1.42 (s, 9H), 1.20 (s, 3H), 1.15 (s, 3H), 1.11 (d, 3H, J = 6.9), 0.86 (d, 3H, J = 6.4), 0.82 (d, 3H, J = 6.4); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176, 170.8, 170.3, 165, 156.5, 153.9, 139, 136.9, 131.7, 131.4, 130.1, 129.5, 128.8, 128.6, 127.5, 126.2, 125.8, 121.9, 111.8, 82.5, 79, 76.5, 71.2, 56.1, 53.7, 48.6, 44, 40.9, 39.5, 36.9, 33.5, 28.4, 28, 24.8, 23.0, 22.8, 22.3, 21.4, 16.7; IR (neat) 3378, 1731, 1677, 1503, 1366, 1257 cm^{-1}; MS (ESI, *m*/*z*) 849.3; HRMS (ESI, *m*/*z*) calcd for $C_{45}H_{63}N_2O_{10}ClNa$ $(M + Na)^+$ 849.4069, found 849.4095.

Cryptophycin 51 (19). To a stirring solution of 117 mg (0.14 mmol) of **18** in 3 mL of CH_2Cl_2 at 0 °C was added 1.6 mL (20.8 mmol) of CF_3COOH slowly. Stirring was continued with warming to room temperature. After 2 h, the solution was concentrated and then reconcentrated with dry toluene to give a white solid. The crude solid was dissolved in 15 mL of DMF, and to this solution was added 68 mg (0.2 mmol) of FDPP in 10 mL of DMF followed by 74 μL (0.43 mmol) of diisopropylethylamine. The yellow solution was stirred at 23 °C under argon. After 12 h, 40 mL of ethyl acetate was added. The organic layer was washed with 40 mL of 1 N HCl, 40 mL of H_2O, and 40 mL of brine and finally dried over Na_2SO_4. After filtration and concentration the crude product was purified by flash silica gel chromatography (45% to 60% ethyl acetate/hexanes) to give 57 mg (61% yield) of macrolactam as a white amorphous solid. $[\alpha]^{23}_D$ +26.2 (*c* 0.5); [lit.[16] $[\alpha]^{23}_D$ +26.4 (*c* 0.25, $CHCl_3$)]; ^1H NMR (400 MHz, $CDCl_3$) δ 7.21−7.33 (m, 6H), 7.2 (d, 1H, J = 1.9), 7.05 (dd, 1H, J = 2.0, 8.4), 6.84 (d, 1H, J = 8.4), 6.77 (ddd, 1H, J = 4.4, 10.8, 15.1), 6.4 (d, 1H, J = 15.8), 6.01 (dd, 1H, J = 8.8, 15.8), 5.75 (d, 1H, J = 15.2), 5.56 (d, 1H, J = 7.8), 5.05 (m, 1H), 4.84 (dd, 1H, J = 3.4, 10.1), 4.74 (dd, 1H, J = 6.6, 13.3 Hz), 3.87 (s, 3H), 3.41 (dd, 1H, J = 8.6, 13.5), 3.12 (d, 1H, J = 3.3 Hz), 3.07−3.09 (m, 2H), 2.55 (m, 2H), 2.38 (ddd, 1H, J = 11, 11.3, 14.3), 1.66 (m, 1H), 1.61 (m, 1H), 1.32 (ddd, 1H, J = 3.5, 8.4, 13.2), 1.22 (s, 3H), 1.15 (s, 3H), 1.13 (d, 3H, J = 6.9), 0.73 (d, 3H, J = 6.9), 0.72 (d, 3H, J = 6.9); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178, 170.5, 170.2, 165, 154, 142.2, 136.5, 131.7, 130.8, 130.1, 129.5, 128.5, 128.2, 127.5, 126.1, 124.4, 122.5, 112.2, 77, 71.4, 56.1, 54.2, 46.4, 42.6, 42.2, 39.4, 36.5, 35.2, 24.5, 22.8, 22.7, 22.6, 21.1, 17.3; IR (neat) 3413, 3276, 1747, 1721, 1658, 1536, 1504, 1259 cm^{-1}; MS (ESI, *m*/*z*) 675.3 $(M + Na)^+$; HRMS (ESI, *m*/*z*) calcd for $C_{36}H_{45}N_2O_7NaCl$ $(M + Na)^+$ 675.2813, found 675.2822.

Cryptophycin 52 (2). To a stirring solution of 53 mg (0.08 mmol) of macrolactam **17** in 5 mL of CH_2Cl_2 at 0 °C was added 29 mg (0.17 mmol) of *m*-CPBA. After dissolution, the ice bath was removed, and stirring was continued with warming to 23 °C for 12 h. The solution was diluted with 25 mL of ethyl acetate, and the organic layer was washed successively with 10 mL of 5% $NaHCO_3$ solution, 10 mL of water, and 10 mL of brine. After drying over Na_2SO_4, filtration, and concentration, the crude product (a 2:1 mixture of epoxides by ^1H NMR) was purified by reverse-phase HPLC (YMC ODS-AQ S5 120 Å, 4.6 mm × 250 mm, 45% H_2O/CH_3CN, λ = 254 nm, 0.9 mL/min; Cryptophycin 52 (**2**) retention time = 53.35 min; Cryptophycin epoxide diastereomer, retention time = 58.25 min, in (38 mg) 70% yield. Cryptophycin 52 (white amorphous solid). $[\alpha]^{23}_D$ +20 (*c* 0.08); [lit.[16] $[\alpha]^{23}_D$ +19.9 (*c* 0.5, $CHCl_3$)]; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33−7.39 (m, 3H), 7.20−7.26 (m, 3H), 7.19 (d, 1H, J = 2.0), 7.05 (dd, 1H, J = 1.9, 8.4), 6.84 (d, 1H, J = 8.4), 6.76 (ddd, 1H, J = 4.3, 10.7, 15), 5.71 (d, 1H, J = 15.2), 5.44 (d, 1H, J = 7.8 Hz), 5.21 (dd, 1H, J = 4.7, 9.6 Hz), 4.82 (dd, 1H, J = 3.4, 10.1), 4.74 (dd, 1H, J = 6.4, 14 Hz), 3.88 (s, 3H), 3.68 (d, 1H, J = 1.6), 3.42 (dd, 1H, J = 8.7, 13.5), 3.11 (d, 1H, J = 3.3), 3.08 (d, 2H, J = 5.7), 2.92 (dd, 1H, J = 1.7, 7.6), 2.58 (m, 1H), 2.45 (ddd, 1H, J = 10.9, 11, 14.4), 1.78 (m, 1H), 1.72 (m, 1H), 1.67 (m, 1H), 1.32 (m, 1H), 1.22 (s, 3H), 1.16 (s, 3H), 1.14 (d, 3H, J = 7.5), 0.85 (d, 3H, J = 6.6), 0.83 (d, 3H, J = 6.6); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.1, 170.5, 170.2, 164.9, 154.1, 141.9, 136.7, 130.9, 129.3, 128.7, 128.6, 128.3, 125.6, 124.6, 122.6, 112.3, 75.9, 71.2, 63.1, 59.1, 56.1, 54.2, 46.4, 42.7, 40.7, 39.3, 36.9, 35.3, 24.6, 22.9, 22.8, 22.7, 21.2, 13.7; IR (neat) 3409, 3263, 1747, 1719, 1653, 1539, 1505, 1259 cm^{-1}; MS (ESI, *m*/*z*) 691.3 $(M + Na)^+$; HRMS (ESI, *m*/*z*) calcd for $C_{36}H_{45}N_2O_8NaCl$ $(M + Na)^+$ 691.2762, found 691.2767.

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Supporting Information Available: Experimental details for compounds **4**, **9**−**11**, ^1H NMR and ^{13}C NMR spectra for compounds **2**, **4**, **5**, **9**−**11**, **13**, **15**, and **18**−**19**. This material is available free of charge via the Internet at http://pubs.acs.org.

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