Synthesis of Cryptophycin 52 Using the Sharpless Asymmetric Dihydroxylation: Diol to Epoxide Transformation Optimized for a Base-Sensitive Substrate

Jian Liang,[†] Eric D. Moher,*[,‡] Richard E. Moore,*[,†] and David W. Hoard[‡]

Department of Chemistry, 2545 The Mall, University of Hawaii, Honolulu, Hawaii 96822, and Chemical Process Research and Development, Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana 46285

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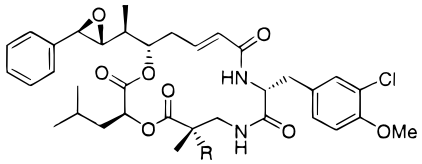
A synthesis of cryptophycin 52 (**2**) is reported using a Sharpless asymmetric dihydroxylation (AD) strategy to install the epoxide moiety. The high stereoselectivity of the AD reaction that allows for an efficient means of preparing the epoxide is in contrast to the standard direct epoxidation of cryptophycin substrates, which proceeds with poor diastereoselectivity. Methodology for conversion of the diol AD product to the requisite epoxide is disclosed. The transformation has been optimized to proceed in high yield in the presence of base sensitive functionality.

The cryptophycins, exemplified by cryptophycin 1 (**1**), are cytotoxic macrocyclic depsipeptides isolated from blue-green algae (Nostoc sp. strains ATCC 537189[1] and GSV 224[2]). Cryptophycin 1 (**1**) has been shown by Moore and co-workers to be a potent tumor-selective cytotoxin in vivo.[2,3] Noteworthy is the broad spectrum of antitumor activity exhibited by **1** across a variety of tumors implanted in mice. Particularly compelling is the observation that **1** significantly reduced the mean tumor burden from a Taxol-resistant mammary adenocarcinoma tumor implanted in mice.[2] The remarkable antiproliferative effects of **1** are believed to be derived from reversible high affinity binding to microtubules, making it one of the most potent suppressors of microtubule dynamics known.[4]



1: R = H
2: R = Me

As a result of these findings, interest in the cryptophycins has blossomed in recent years with numerous reports highlighting the biological evaluation of new synthetic analogues.[5] From our efforts, in collaboration with Wayne State University, aimed at discovering and developing cryptophycin analogues possessing refined biological properties, has emerged cryptophycin 52 (**2**).[6] Cryptophycin 52, designed to enhance hydrolytic stability[3] relative to **1** while maintaining a favorable profile of antitumor activity, is in clinical development for the treatment of solid tumors.

Additionally, several research groups have adopted programs aimed at addressing the synthetic challenges associated with this structurally intriguing class of molecules. The first reports on the total synthesis of cryptophycins appeared in 1994 from the research groups of Kitigawa,[7] Moore, and Tius.[8] These were soon followed by numerous approaches comprised of both formal and total syntheses.[9] A common strategical thread running through the majority of syntheses of epoxide-containing cryptophycins (e.g., **1**) has been the introduction of the epoxide pharmacophore in a single late-stage operation (vide infra). The epoxidation proceeds with a diastereoselectivity of 2−3:1 necessitating a tedious chromatographic separation of the desired (major) β-isomer. Typical isolated yields are reported in the 50−55% range,

[†] University of Hawaii.
[‡] Eli Lilly and Company.

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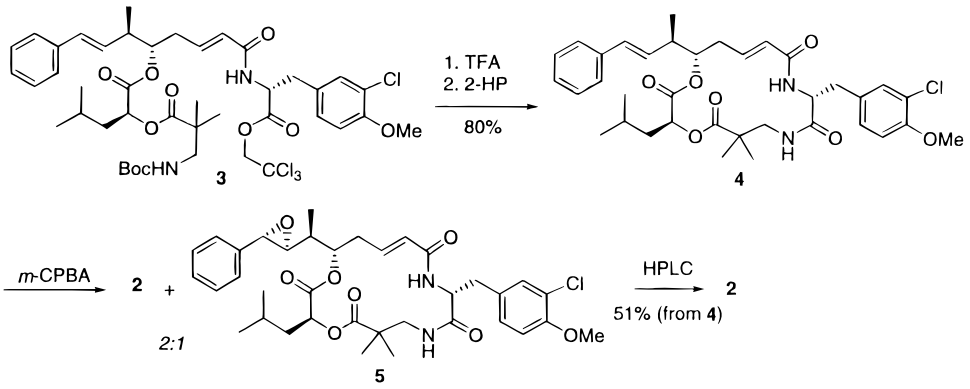
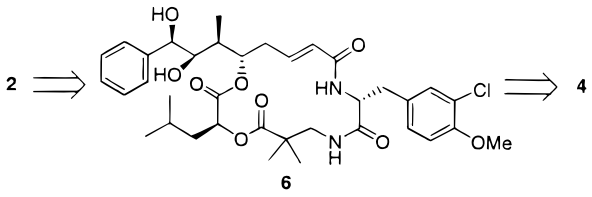
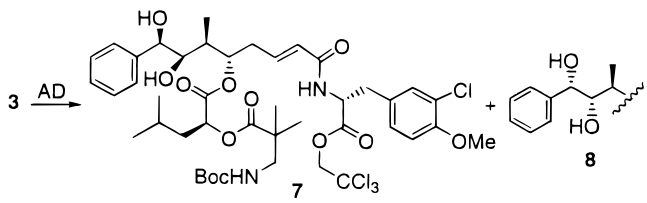
Scheme 1



Scheme 2



Scheme 3



making this transformation the Achilles heal of the synthesis in terms of efficiency and throughput. One notable exception is Leahy's elegant synthesis of **1** featuring an auxiliary based diastereoselective aldol reaction leading to a syn-1,2-β-diol as an epoxide precursor.[9g] Elaboration of the diol to epoxide **1** proceeded by way of a novel variation on the Sharpless ortho ester method.[10]

As part of our initial efforts to generate supplies of **2** and synthetic intermediates to fuel clinical development and SAR, respectively, we adopted the Moore−Tius synthesis of **2**,[6a,8] making necessary adjustments for multikilo operations. The final synthetic sequence[11] (Scheme 1) culminates in an epoxidation employing *m*-CPBA to produce a 2:1 mixture of epoxides **2** and **5** from which **2** is isolated in 51% yield by reversed-phase HPLC. Clearly we required a more efficient means for generating the epoxide since the transformation, due to its poor diastereoselectivity, was a bottleneck that hampered our ability to generate sufficient quantities of **2**.

Sharpless has shown that syn-vicinal diols serve as epoxide precursors capable of being masked and carried through several synthetic operations prior to revealing the potentially sensitive oxirane.[10,12] With the advent of the Sharpless asymmetric dihydroxylation (AD) protocol, a wide variety of olefins can be enantio- and diastereoselectively transformed into *syn*-1,2-diols and thus to epoxides in good yield over a three- to four-step sequence.[13] In analogy to the Leahy synthesis,[9g] we envisioned the conversion of diol **6** to epoxide **2** (Scheme 2); however, we were intrigued by the potential for a stereoselective dihydroxylation of styrene **4**, an overall strategy in keeping with the familiar protocols of the Moore−Tius route yet obviating the inefficient epoxidation reaction.

Table 1. Stoichiometry Study for the AD of 3

entry	$K_2OsO_2(OH)_4$ (mol %)	ligand (mol %)	K_2CO_3 (equiv)	time (h)	**7** (% yield)[a]
1	2	4	3	3.5	55
2	2	2	3	4	55
3	1	2	3	5.5	53
4	1	1	3	27	30
5	2	2	2	20.5	61
6	1	2	2.3	9	57
7	2	2	4	3.5	48
8	2	2	3 (+3 $NaHCO_3$)	20	60

[a] Isolated yield after flash chromatography.

Initial attempts to stereoselectively dihydroxylate **4** using OsO_4, catalytic[14] or stoichiometric, gave approximately equal mixtures of four diastereomers resulting from indiscriminate stereofacial and regiochemical attack of the reagent on the two olefins. Ruthenium-catalyzed cis-dihydroxylation according to the method of Shing[15] led to rapid degradation of **4** with production of aldehydic components as evidenced by ^{1}H NMR. Equally discouraging was the AD using the dihydroquinidine based phthalazine ligand $(DHQD)_2PHAL$, which proved completely ineffective due to the insolubility of **4** in the standard AD solvent system (t-BuOH/H_2O).

With the selective dihydroxylation of **4** appearing unfeasible, we moved to a modified strategy employing a more tractable substrate. To our satisfaction, the AD of styrene **3** (Scheme 3) employing $(DHQD)_2PHAL$ in the presence of catalytic $K_2OsO_2(OH)_4$ proceeded in moderate yield to produce diols **7** and **8** with high diastereoselectivity (29:1) favoring β-diol **7**. Table 1 summarizes the results of a study aimed at optimizing the yield of **7** while minimizing the amount of ligand and osmium used. The reactions were conducted in t-BuOH/H_2O (1:1, 0.1 M in olefin) at room temperature with added $MeSO_2NH_2$ (1 equiv) as an accelerant, $K_3Fe(CN)_6$ (3 equiv) as stoichiometric oxidant, and K_2CO_3 as base to facilitate osmate

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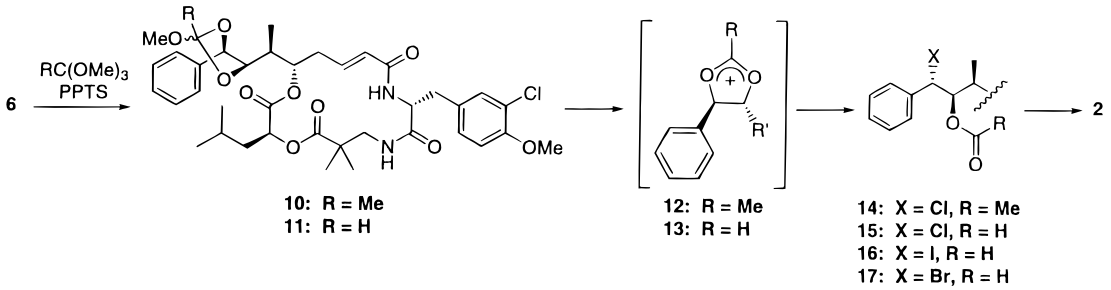
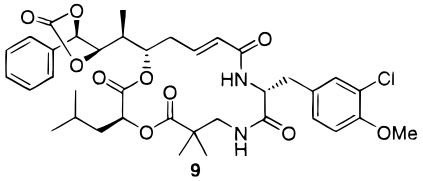
Scheme 4



ester hydrolysis.[13] From the results in Table 1 two general features of the reaction become apparent: (1) styrene **3** reacts sluggishly with low osmium and ligand loading (entry 1−3 vs 4), in contrast to many olefins that require as little as 0.2 mol % Os and 1 mol % ligand for high conversion; (2) the yield is compromised by the base-sensitive nature of the substrate (entry 5 vs 7). Decreasing both osmium and ligand loading results in a sluggish reaction giving rise to inferior yields since prolonged exposure of the product and starting material to the basic reaction conditions is detrimental (entry 4). These two trends, which work in concert, dictate loading of the expensive osmium and cinchona alkaloid-based ligand to a lower limit of 2−4 mol %. Unfortunately, buffering the reaction (entry 8), employing a slow addition of base (not shown), or adding excess $MeSO_2NH_2$ (not shown) did not lead to significantly increased yields.

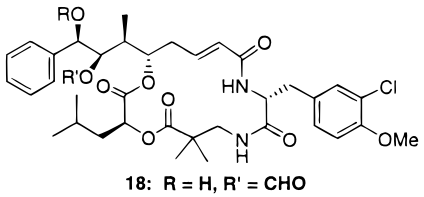
With *seco*-diol **7** in hand, we were ready to carry out the macrolactamization. This was conducted uneventfully according to a modification of the Fray protocol[11] for cyclization of *seco*-styrene **3**. Namely, **7** was treated with TFA (15 equiv) to effect *tert*-butyl carbamate cleavage followed by workup with K_2CO_3, which afforded the intermediate amine as an amorphous solid. Dissolution of the amine in acetonitrile−toluene and treatment with 2-hydroxypyridine (2HP, 2 equiv) afforded an 82% yield of macrocycle **6** after flash chromatography. It is noteworthy that exposure of unprotected **7** to TFA does not result in pinacol rearrangement or epimerization due to S_N1 reactions at the benzylic hydroxyl-bearing methine.

Having access to macrocyclic diol **6**, the stage was set for the critical diol to epoxide conversion and elaboration to **2**. Initial studies focused on carbonate **9** drawing from literature precedent provided by Sharpless,[16] who showed that heating the carbonate derived from stilbene diol in the presence of LiCl smoothly provided stilbene oxide in 84% yield. In the event, **9** and LiCl (1−2 equiv) were heated in DMF for 9 h to afford a 25% yield of epoxide **2** and 25% recovered **9** with the balance comprised of unknown decomposition products. Clearly, at elevated temperatures the molecule suffers decomposition at a rate competitive with chloride ion displacement of CO_2. Other attempts were made using LiI[17] (DMF and pyridine as solvents), TMSI,[18] and TMSCl resulting primarily in recovered carbonate.



The carbonate approach was abandoned for the alternative three-step procedure involving the ionization of an ortho ester and opening of the resulting 1,3-dioxolan-2-ylium ion intermediate (e.g., **12**) by halide ion to provide a vicinal acetoxy halide species.[12] Subsequent saponification with spontaneous cyclization would lead to the desired epoxide. Toward this end, orthoacetate **10** was treated with TMSCl giving rise (via **12**) to acetoxy chloride **14** in nearly quantitative yield as a single isomer (Scheme 4). In keeping with Leahy's observations,[9g] exposure of **14** to a variety of basic hydrolysis conditions (K_2CO_3-methanol, LiOH, *n*-Bu_4NOH) resulted in decomposition of the material owing to indiscriminate ester cleavage. Best results were obtained using in situ generated lithium hydroperoxide[19] giving **2** directly in 50% isolated yield. The base sensitive nature of the cryptophycins necessitated an alternative yet concise and economical method for the diol to epoxide conversion.

Critical to enabling a successful ortho ester strategy was to employ an ester more labile than acetate or any of the other ester linkages comprising the cryptophycin framework. It was believed that a formate ester would meet this requirement and allow efficient access to epoxide **2**. Treatment of orthoformate **11** with TMSCl failed to produce any of the desired formyloxy chloride **15**, but instead only hydroxy formates **18** and **19** were formed presumably by kinetic trapping of the putative intermediate 1,3-dioxolan-2-ylium ion **13** at the 2-position by chloride ion with eventual hydrolysis by adventitious water.



To our great satisfaction, reaction of **11** with TMSI produced formyloxy iodide **16** in 93% yield over the two steps (Scheme 4). Formate **16** could subsequently be saponified and cyclized producing epoxide **2** with high efficiency. The conversion is best accomplished with $KHCO_3$ or K_2CO_3 in methanol−tetrahydrofuran (93% and 98% yield, respectively) while lithium hydroperoxide gave

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an inferior yield of 67%. The expense of TMSI led us to look for an alternative reagent for the rearrangement of **11**. We were pleased to find that acetyl bromide is sufficiently reactive to provide formyloxy bromide **17** in 85% yield for the two-step sequence. Conversion of **17** to **2** follows in a similar high-yielding manner to that described for **16**.

Similar diol to *vic*-formyloxy halide transformations have appeared in the literature; however, they have rarely been applied in organic synthesis.[20] For example, Hartman[20c] and Baganz[20d] have reported on the preparation of formyloxy chlorides by heating orthoformates derived from simple 1,2-diols in the presence of acetyl chloride. Additionally, limited examples exist where the treatment of orthoformates with PCl_5 affords fomyloxy chlorides in good yield.[20a,b] Thus, borrowing from the work of Nicolaou,[20b] **11** was treated with PCl_5 giving rise to formyloxy chloride **15**, however, in a disappointingly low yield (18%).

In conclusion, a synthesis of cryptophycin 52 (**2**) has been demonstrated on the basis of the Sharpless asymmetric dihydroxylation (AD), which provides an efficient method of installing the cryptophycin epoxide moiety. The route circumvents the commonly employed direct last step epoxidation which exhibits poor diastereoselectivity and necessitates a preparative HPLC isolation. Experiments are currently underway exploring the scope and generality of the methodology disclosed herein for the mild diol to epoxide transformation.

Experimental Section

General Procedures. ^{1}H and ^{13}C NMR spectra were recorded on a 500 MHz spectrometer. Melting points are uncorrected. Reactions were monitored by TLC (*p*-anisaldehyde stain) and HPLC equipped with a 4.6 mm × 250 mm Zorbax SB-C18 column (1 mL/min, acetonitrile−water both with 0.5% TFA) with detection at 220 nm. Elemental analyses and infrared (FTIR) spectra were performed at the Structural and Organic Chemistry Research Laboratory, Eli Lilly and Company, Indianapolis, IN.

***seco*-Diol 7**. To a mixture of *seco*-styrene **3** (304 mg, 0.34 mmol), $K_2OsO_2(OH)_4$ (2.5 mg, 0.0067 mmol), $(DHQD)_2PHAL$ (5.2 mg, 0.0067 mmol), $K_3Fe(CN)_6$ (333 mg, 1.01 mmol), K_2CO_3 (93 mg, 0.67 mmol), and $MeSO_2NH_2$ (32 mg, 0.34 mmol) was added 0.615 mL of *t*-BuOH and 0.615 mL of H_2O. The heterogeneous mixture was allowed to stir rapidly at room temperature for 20.5 h. The reaction was treated with 304 mg of Na_2SO_3. After being stirred for 25 min, the mixture was diluted with 3 mL of H_2O and washed with ethyl acetate. The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated in vacuo to an off-white oil. Chromatography (34 g of flash SiO_2) eluting with ethyl acetate−hexanes (1:1 then 2:1) provided 193 mg (61%) of **7** as a white amorphous solid: R_f 0.54 (2:1/ethyl acetate/hexanes); $[\alpha]^{25}_D$ −52° (*c* 1.14, $CHCl_3$); 500 MHz ^{1}H NMR ($CDCl_3$) δ 7.41−7.31 (m, 5H), 7.18 (s, 1H), 7.07 (d, 1H, J = 8.2 Hz), 6.85 (d, 1H, J = 8.2 Hz), 6.60−6.63 (m, 1H), 6.53 (d, 1H, J = 7.8 Hz), 5.74 (d, 1H, J = 16 Hz), 5.28 (t, 1H, J = 6.2 Hz), 5.07−4.99 (m, 2H), 4.94 (dd, 1H, J = 9.9, 3.2 Hz), 4.80 and 4.72 (AB quartet, 2H, J = 12 Hz), 4.63 (d, 1H, J = 8.1 Hz), 3.88 (s, 3H), 3.65−3.60 (m, 1H), 3.30 (d, 2H, J = 6.5 Hz), 3.21 (dd, 1H, J = 14, 6.8 Hz), 3.07 (dd, 1H, J = 14, 5.8 Hz), 3.00 (d, 1H, J = 3.5 Hz), 2.96 (s, 1H), 2.54−2.60 (m, 1H), 2.41−2.34 (m, 1H), 1.90−1.77 (m, 2H), 1.65−1.58 (m, 1H), 1.57−1.41 (m, 1H), 1.46 (s, 9H), 1.23 (s, 3H), 1.18 (s, 3H), 1.03−0.99 (m, 6H), 0.97 (d, 3H, J = 6.5 Hz); 125 MHz ^{13}C NMR ($CDCl_3$) δ 177.42, 172.28, 170.37, 165.63, 156.72, 154.52, 140.58, 139.64, 131.59, 129.29, 129.13, 128.85, 127.40, 125.49, 122.68, 112.54, 94.75, 79.59, 76.38, 75.64, 75.03, 74.88, 71.72, 56.50, 53.64, 49.03, 44.39, 39.95, 38.09, 36.96, 33.94, 28.80, 25.40, 23.57, 23.20, 22.80, 21.88, 9.94; FTIR (KBr) 3390 (s), 2974 (s), 1725 (s), 1678 (m), 1641 (m), 1504 (s), 1259 (s), 1151 (s) cm^{-1}. Anal. Calcd for $C_{43}H_{58}Cl_4N_2O_{12}$: C, 55.13; H, 6.24; N, 2.99. Found: C, 55.38; H, 6.39; N, 2.99.

Macrocyclic Diol 6. To a solution of **7** (1.32 g, 1.41 mmol) in 2.8 mL of CH_2Cl_2 at 0 °C was added TFA (1.62 mL, 21.1 mmol). After being stirred for 1.5 h, the reaction mixture was poured into a solution of K_2CO_3 (4.8 g, 34.7 mmol) in 8.4 mL of water. The layers were separated, and the aqueous layer was washed with ethyl acetate. The combined organics were washed with H_2O, dried (Na_2SO_4), filtered, and concentrated in vacuo to a faint brown oil. The crude amine was dissolved in 22.5 mL of acetonitrile, diluted with 22.5 mL of toluene, and treated with 2-hydroxypyridine (268 mg, 2.82 mmol). The mixture was heated to 40 °C and stirred for 21 h, after which time it was diluted with 15 mL of ethyl acetate, washed with saturated aqueous $NaHCO_3$, washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo to a faint brown oil. Chromatography (30 g of flash SiO_2) eluting with ethyl acetate provided 793 mg (82%) of **6** as a white solid: R_f 0.36 (ethyl acetate); 500 MHz ^{1}H NMR ($CDCl_3$) δ 7.51−7.31 (m, 5H), 7.22 (d, 1H, J = 2.0 Hz), 7.19−7.15 (m, 1H), 7.07 (dd, 1H, J = 8.4, 2.0 Hz), 6.86 (d, 1H, J = 8.4 Hz), 6.74 (ddd, 1H, J = 15, 11, 3.7 Hz), 5.72, (dd, 1H, J = 15, 1.2 Hz), 5.58 (d, 1H, J = 7.9 Hz), 5.12−5.08 (m, 1H), 6.18 (dd, 1H, J = 9.9, 3.7 Hz), 4.77−4.72 (m, 1H), 4.60 (d, 1H, J = 8.4 Hz), 3.90 (s, 3H), 3.80 (d, 1H, J = 8.4 Hz), 3.38 (dd, 1H, J = 13.5, 8.1 Hz), 3.20 (dd, 1H, J = 13.5, 3.9 Hz), 3.13 (dd, 1H, J = 14.5, 5.2 Hz), 3.05 (dd, 1H, J = 14.5, 7.6 Hz), 2.83 (br s, 1H), 2.78 (br s, 1H), 2.52−2.47 (m, 1H), 2.28−2.20 (m, 1H), 1.86−1.80 (m, 1H), 1.72−1.65 (m, 1H), 1.54−1.44 (m, 2H), 1.25 (s, 3H), 1.19 (s, 3H), 1.03 (d, 3H, J = 7.0 Hz), 0.97 (d, 3H, 6.7 Hz), 0.91 (d, 3H, J = 6.5 Hz); 500 MHz ^{1}H NMR (CD_3OD) δ 7.40−7.35 (m, 5H), 7.34−7.30 (m, 1H), 7.27 (d, 1H, J = 2.1 Hz), 7.16 (dd, 1H, J = 8.4, 2.1 Hz), 6.98 (d, 1H, J = 8.4 Hz), 6.69 (ddd, 1H, J = 15, 13, 3.8 Hz), 5.85 (dd, 1H, J = 15, 1.6 Hz), 5.10 (br t, 1H, J = 9.7 Hz), 4.93 (dd, 1H, J = 10, 3.5 Hz), 4.55 (d, 1H, J = 8.3 Hz), 4.51 (dd, 1H, J = 11, 3.7 Hz), 3.85 (s, 3H), 3.73 (dd, 1H, 8.3, 1.6 Hz), 3.46 (d, 1H, 14 Hz), 3.18 (dd, 1H, J = 14, 3.7 Hz), 3.10 (d, 1H, J = 14 Hz), 2.73 (dd, 1H, J = 14, 11 Hz), 2.66−2.59 (m, 1H), 2.18−2.09 (m, 1H), 1.85−1.78 (m, 1H), 1.75−1.66 (m, 1H), 1.60−1.52 (m, 1H), 1.49−1.41 (m, 1H), 1.22 (s, 3H), 1.19 (s, 3H), 1.02−0.97 (m, 6H), 0.95 (d, 3H, J = 6.6 Hz); 125 MHz ^{13}C NMR (CD_3OD) δ 177.83, 172.70, 170.78, 167.23, 154.37, 143.23, 142.32, 131.19, 130.47, 128.52, 128.25, 128.00, 127.13, 124.04, 122.28, 112.53, 76.20, 76.12, 74.88, 71.47, 56.44, 55.61, 46.41, 43.09, 39.92, 38.77, 36.52, 35.44, 25.08, 22.41, 22.39, 22.29, 20.98, 8.67; FTIR (KBr) 3419 (m), 3280 (m), 1752 (s), 1721 (s), 1663 (s), 1503 (s), 1257 (s), 1196 (s), 1151 (s) cm^{-1}. An analytical sample was prepared by crystallization from ethyl acetate: mp 144−145 °C; $[\alpha]^{25}_D$ −34° (*c* 1.00, MeOH). Anal. Calcd for $C_{36}H_{47}ClN_2O_9$: C, 62.92; H, 6.89; N, 4.08. Found: C, 62.66; H, 6.73; N, 4.00.

Acetoxy Chloride 14. To a slurry of **6** (33 mg, 0.048 mmol) and pyridinium *p*-toluenesulfonate (1.2 mg, 0.0048 mmol) in 0.096 mL of CH_2Cl_2 at room temperature was added trimethyl orthoacetate (0.061 mL, 0.48 mmol). After being stirred for 1 h, the reaction was applied directly to a chromatography column (13 g of flash SiO_2) eluting with ethyl acetate−hexanes (5:1) to provide 34 mg (94%) of **10** as a white amorphous solid. To a solution of **10** (33 mg, 0.044 mmol) in 0.222 mL of CH_2Cl_2 at room temperature was added TMSCl (0.0068 mL, 0.053 mmol). After being stirred for 2.5 h, the reaction was concentrated in vacuo to provide 32 mg (97%) of **14** as a white amorphous solid: R_f 0.43 (5:1/ethyl acetate/hexanes); 500 MHz ^{1}H NMR ($CDCl_3$) δ 7.38−7.31 (m, 5H), 7.24 (d, 1H, J = 2.1 Hz), 7.22−7.18 (m, 1H), 7.10 (dd, 1H, J = 8.5, 2.1 Hz), 6.88 (d, 1H, J = 8.5 Hz), 6.75 (ddd, 1H, J = 15, 13, 4.6 Hz), 5.78 (dd, 1H, J = 15, 1.0 Hz), 5.55 (d, 1H, J = 7.9 Hz), 5.46 (dd, 1H, J = 9.8, 1.2 Hz), 4.95 (dd, 1H, J = 11, 2.9 Hz), 4.89 (ddd, 1H, J

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= 9.9, 9.9, 1.7 Hz), 4.81 (d, 1H, J = 9.8 Hz), 4.79−4.74 (m, 1H), 3.91 (s, 3H), 3.39 (dd, 1H, J = 13, 8.1 Hz), 3.22 (dd, 1H, J = 13, 4.1 Hz), 3.16 (dd, 1H, J = 14, 5.1 Hz), 3.07 (dd, 1H, J = 14, 7.6 Hz), 2.65−2.55 (m, 2H), 2.47−2.39 (m, 1H), 1.95 (ddd, 1H, J = 14, 13, 4.6 Hz), 1.86−1.77 (m, 1H), 1.73−1.66 (m, 1H), 1.68 (s, 3H), 1.27 (s, 3H), 1.19 (s, 3H), 1.09 (d, 3H, J = 7.1 Hz), 1.03 (d, 3H, J = 6.7 Hz), 0.97 (d, 3H, J = 6.6 Hz).

Formyloxy Iodide 16. To a slurry of **6** (144 mg, 0.210 mmol) and pyridinium *p*-toluenesulfonate (2.6 mg, 0.010 mmol) in 0.698 mL of CH_2Cl_2 at room temperature was added trimethyl orthoformate (0.229 mL, 2.10 mmol). After being stirred for 2.5 h, the reaction was treated with 1 mL of saturated aqueous $NaHCO_3$ and washed with ethyl acetate. The combined organics were dried (Na_2SO_4), filtered, and concentrated in vacuo to provide 153 mg of **11** as a white amorphous solid that was used directly in the next experiment. To a solution of crude **11** from above in 1.4 mL of CH_2Cl_2 at 0 °C was added TMSI (0.045 mL, 0.315 mmol). After being stirred for 45 min, the reaction was quenched with 1 mL of saturated aqueous $NaHCO_3$ followed by 0.5 mL of 10% aqueous $Na_2S_2O_3$ and washed with ethyl acetate. The combined organics were dried (Na_2SO_4), filtered, and concentrated in vacuo to a faint yellow amorphous solid. Chromatography (15 g of flash SiO_2) eluting with ethyl acetate:hexanes (3:1) gave 161 mg (93%) of **16** as a faint yellow foam: R_f 0.42 (3:1/ethyl acetate/hexanes); 500 MHz ^{1}H NMR ($CDCl_3$) δ 7.61 (s, 1H), 7.41−7.18 (m, 7H), 7.10 (dd, 1H, J = 8.4 Hz, 2.0 Hz), 6.87 (d, 1H, J = 8.4 Hz), 6.76 (ddd, 1H, J = 15, 11, 4.6 Hz), 5.88 (d, 1H, J = 10 Hz), 5.81 (d, 1H, J = 15 Hz), 5.66 (d, 1H, J = 7.9 Hz), 5.07 (d, 1H, J = 10 Hz), 4.99 (dd, 1H, J = 11, 3.0 Hz), 4.93−4.87 (m, 1H), 4.79−4.72 (m, 1H), 3.90 (s, 3H), 3.39 (dd, 1H, J = 13, 8.0 Hz), 3.23 (dd, 1H, J = 13, 3.9 Hz), 3.16 (dd, 1H, J = 14, 5.1 Hz), 3.07 (dd, 1H, J = 14, 7.8 Hz), 2.90−2.83 (m, 1H), 2.63−2.58 (m, 1H), 2.51−2.43 (m, 1H), 2.02−1.96 (m, 1H), 1.86−1.53 (m, 2H), 1.28 (s, 3H), 1.20 (s, 3H), 1.05 (d, 6H, J = 6.7 Hz), 0.98 (d, 3H, J = 6.4 Hz); 125 MHz ^{13}C NMR (CD_3OD) δ 178.22, 170.80, 170.48, 165.51, 159.12, 154.46, 142.08, 139.86, 131.33, 130.22, 129.04, 128.98, 128.81, 128.68, 125.18, 122.93, 112.77, 75.49, 73.88, 71.63, 56.57, 54.88, 47.00, 43.27, 40.22, 40.06, 37.12, 35.73, 31.29, 25.35, 23.59, 23.32, 23.19, 21.92, 10.52; FTIR (KBr) 3421 (m), 3275 (m), 1758 (s), 1727 (s), 1674 (s), 1538 (s), 1504 (s), 1151 (s) cm^{-1}. An analytical sample was prepared by crystallization from ethyl acetate/heptane: mp 144−146 °C; $[\alpha]^{25}_D$ +84° (*c* 1.09, $CHCl_3$). Anal. Calcd for $C_{37}H_{46}ClIN_2O_9$: C, 53.86; H, 5.62; N, 3.39. Found: C, 53.76; H, 5.56; N, 3.39.

Cryptophycin 52 (2) from 16 with K_2CO_3. To a solution of **16** (55 mg, 0.067 mmol) in 0.138 mL of THF and 0.412 mL of MeOH was added $KHCO_3$ (33 mg, 0.333 mmol). The heterogeneous mixture was allowed to stir at 43 °C for 14.5 h. The reaction was diluted with H_2O (0.5 mL) and washed with ethyl acetate. The combined organics were dried (Na_2SO_4), filtered, and concentrated in vacuo to a yellow foam. Chromatography (12 g of flash SiO_2) eluting with ethyl acetate:heptane (3:1) afforded 42 mg (93%) of **2**[6a] as a white solid.

Cryptophycin 52 (2) from 16 with Potassium Carbonate. To a solution of **16** (73 mg, 0.088 mmol) in 0.295 mL of THF and 0.295 mL of MeOH was added K_2CO_3 (18 mg, 0.133 mmol). The heterogeneous mixture was allowed to stir at 0 °C for 6 h. The reaction was diluted with ethyl acetate (1 mL) and pH 7 buffer (1 mL). The layers were separated, and the aqueous layer was washed with ethyl acetate. The combined organics were dried (Na_2SO_4), filtered, and concentrated in vacuo to a yellow foam. Chromatography (13 g of flash SiO_2) eluting with ethyl acetate/heptane (3:1) afforded 58 mg (98%) of **2**[6a] as a white solid.

Formyloxy Bromide 17. To a slurry of **6** (144 mg, 0.210 mmol) and pyridinium *p*-toluenesulfonate (2.6 mg, 0.010 mmol) in 0.698 mL of CH_2Cl_2 at room temperature was added trimethyl orthoformate (0.229 mL, 2.10 mmol). After being stirred for 2.5 h, the reaction was treated with 1 mL of saturated aqueous $NaHCO_3$ and washed with ethyl acetate. The combined organics were dried (Na_2SO_4), filtered, and concentrated in vacuo to provide 166 mg of **11** as a white amorphous solid that was used directly in the next experiment. To a solution of crude **11** from above in 1.4 mL of CH_2Cl_2 at room temperature was added acetyl bromide (0.031 mL, 0.420 mmol). After being stirred for 140 min, the reaction was quenched with saturated $NaHCO_3$ (1 mL) and washed with ethyl acetate. The combined organics were dried (Na_2SO_4), filtered, and concentrated in vacuo to an off-white foam. Chromatography (15 g of flash SiO_2) eluting with ethyl acetate/hexanes (3:1) gave 139 mg (85%) of **17** as a white solid: R_f 0.42 (3:1/ethyl acetate/hexanes); 500 MHz ^{1}H NMR ($CDCl_3$) δ 7.62 (s, 1H), 7.39−7.28 (m, 5H), 7.24 (d, 1H, J = 1.9 Hz), 7.21−7.18 (m, 1H), 7.10 (dd, 1H, J = 8.4, 1.9 Hz), 6.88 (d, 1H, J = 8.4 Hz), 6.76 (ddd, 1H, J = 15, 11, 4.7 Hz), 5.79 (d, 1H, J = 15 Hz), 5.78 (d, 1H, J = 10 Hz), 5.53 (d, 1H, J = 7.9 Hz), 4.97 (dd, 1H, J = 11, 3.0 Hz), 4.93−4.87 (m, 1H), 4.90 (d, 1H, J = 10 Hz), 4.79−4.72 (m, 1H), 3.91 (s, 3H), 3.38 (dd, 1H, J = 13, 7.9 Hz), 3.24 (dd, 1H, J = 13, 3.9 Hz), 3.17 (dd, 1H, J = 14, 5.1 Hz), 3.08 (dd, 1H, J = 14, 7.6 Hz), 2.81−2.76 (m, 1H), 2.63−2.58 (m, 1H), 2.51−2.42 (m, 1H), 2.01−1.93 (m, 1H), 1.86−1.68 (m, 2H), 1.27 (s, 3H), 1.20 (s, 3H), 1.10 (d, 3H, J = 7.0 Hz), 1.04 (d, 3H, J = 6.7 Hz), 0.99 (d, 3H, J = 6.5 Hz); 125 MHz ^{13}C NMR ($CDCl_3$) δ 178.18, 170.81, 170.50, 165.52, 158.99, 154.46, 142.07, 137.87, 131.33, 130.24, 129.48, 128.97, 128.88, 128.67, 125.19, 122.92, 112.77, 75.37, 73.31, 71.60, 56.56, 54.90, 52.27, 47.00, 43.26, 40.03, 39.13, 37.16, 35.73, 25.32, 23.57, 23.32, 23.28, 21.88, 10.56; FTIR (KBr) 3421 (m), 3265 (m), 1758 (s), 1728 (s), 1674 (s), 1504 (s), 1150 (s) cm^{-1}. An analytical sample was prepared by crystallization from ethyl acetate/heptane: mp 153−155 °C; $[\alpha]^{25}_D$ +73° (*c* 1.05, $CHCl_3$). Anal. Calcd for $C_{37}H_{46}ClBrN_2O_9$: C, 56.82; H, 5.91; N, 3.65. Found: C, 57.11; H, 5.96; N, 3.60.

Cryptophycin 52 (2) from 17 with Potassium Bicarbonate. The procedure was identical to the analogous method for the convesion of **16** to **2**. Here, 47 mg (0.060 mmol) of **17** afforded 37 mg (93%) of **2**[6a] as a white solid.

Cryptophycin 52 (2) from 17 with Potassium Carbonate. The procedure was identical to the analogous method for the convesion of **16** to **2**. Here, 56 mg (0.072 mmol) of **17** afforded 45 mg (94%) of **2**[6a] as a white solid.

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