Discovery through Total Synthesis: A Retrospective on the Himastatin Problem

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Dedicated to Albert Eschenmoser

Abstract: A total synthesis of a structure proposed for himastatin was accomplished. The non-identity of the fully synthetic material with himastatin necessitated a revision of the assigned structure. Confirmation of the revised stereostructure was subsequently confirmed through total synthesis. Among the achievements during this effort were i) stereospecific routes to both *anti–cis* and *syn–cis* pyrrolindoline substructures; ii) a practical synthesis to 5-hydroxypiperazic acid in enantiomerically pure form; iii) a Stille coupling leading to a complex bi-indole moiety, and iv) efficient protecting group management throughout the evolving depsipeptide domain. The outlines for a biological pharmacophore have been delineated. The alternating D- and L-substituents in the 6-mer as well as the biaryl linkage connecting the two identical subunits are critical for maintaining biological activity. This pattern is simulated in another antibiotic, and suggests a possible structural trend for future SAR investigations.

Keywords: antibiotics · himastatin · natural products · protecting groups · total synthesis

Introduction

Given the growing need for new antibiotic agents in the ongoing battle against microbial infection, the screening of multiple potential sources of useful metabolites continues. Clearly, the increasingly serious consequences associated with the emergence of new strains of microorganisms which are resistant to the menu of known bactericides heightens interest in this important area.[1] There is a particularly acute need for antibiotics of novel structure which lend themselves to further structural diversification for purposes of combating resistance. Undoubtedly, these sorts of considerations loomed large in directing researchers from the Bristol Myers Laboratories to the Himachal Pradesh State in India and to the study of an indigenous actinomycete strain. During the course of this venture, the isolation team had characterized an apparently new metabolite of the formula $C_{72}H_{104}N_{14}O_2$.[2a, b] In keeping with the history and geographic setting of the project, as well as the antibacterial (gram positive) and antitumor properties the new agent was termed himastatin.

There then ensued a program of strain improvement and corresponding upgrading of fermentation yield. In parallel, an effort directed to establishing the structure of himastatin was launched. Extensive hydrolytic studies served to identify the components of the depsipeptide, which joins to an oxidatively modified tryptophan. Attention was next directed to the linkage order of the subunits. Mass spectrometry served to fill in some of the missing elements in the structural puzzle. Most critical to the analysis, was the creative use of state of the art interactive ^1H and ^{13}C NMR spectroscopy. At the chemical level, a major advance was accomplished by treatment of himastatin with lithium borohydride (Figure 1). The major

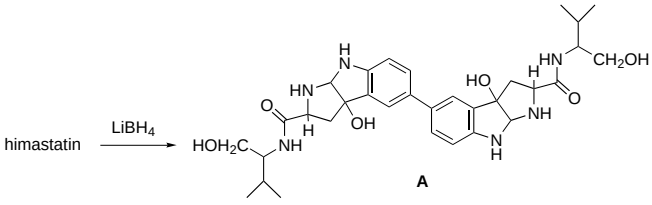

Figure 1. Himastatin degradation product.

product resulting from this protocol, $C_{22}H_{44}N_6O_6$ bearing a single valinol residue per subunit, lent itself to more detailed analysis. At this stage the presence of a symmetric, oxidatively dimerized version of a hypothetical monomer (vide infra) could be formulated, which contains an oxidatively cyclized tryptophan subunit. The site of oxidative dimerization was in the benzo region of the indole, while oxidative cyclization had occurred in its pyrrolo sector. The C terminus of the modified tryptophan serves to acylate a D-valinol residue (see gross structure **A**).

Starting from a secure assignment of the D-valine configuration at the side chain in **A**, ORD measurements in concert

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with extensive NMR measurements led the Bristol Myers scientists to assign the pyrroloindoline moiety to the D-tryptophan series, and to assert an *anti* relationship of the tryptophan derived carboxamido function and the *cis*-fused junction substituents (Figure 2). The N_b of the tryptophan derived pyrroloindole is joined in an amidic linkage to a D-threonine residue. The *summation* of these arguments led to the advancement of structure **1** to himastatin and structure **2** to product **A** arising from reduction of the natural product with lithium borohydride.[2c]

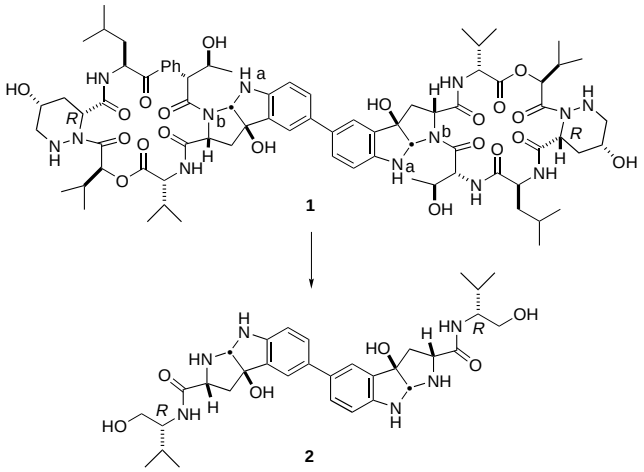

Figure 2. Proposed structures for himastatin and degradation product.

Results and Discussion

Key issues: Given our longstanding interest in the synthesis of various pyrroloindole alkaloids,[3] the promising antibiotic activity reported for himastatin,[2a] and its nonconventional structural features, we were naturally drawn to this molecule as a focusing target for a study in total synthesis. From the outset, there was no doubt that such a total synthesis venture would prove to be difficult. However, we hoped and expected that there could be correspondingly favorable learning opportunities. The lessons so garnered could well go beyond the particulars of himastatin.[4, 5]

Included in the program was the goal of establishing whether the bacteriocidal activity of himastatin arises from the core monomer alone, or whether some form of intramolecular collaboration between the identical subgroups in the "dimer" is critical. We also hoped to undertake a more subtle, but related inquiry, that is, whether there is a long-range communication between the two identical domains, which could be detected at the spectroscopic level. To deal with these questions, it would be necessary to gain access to the "monomer-like" system **3** and further evaluation with regard to activity as well as congruency of its depsipeptide domains with respect to those of **1** (Figure 3). Since the

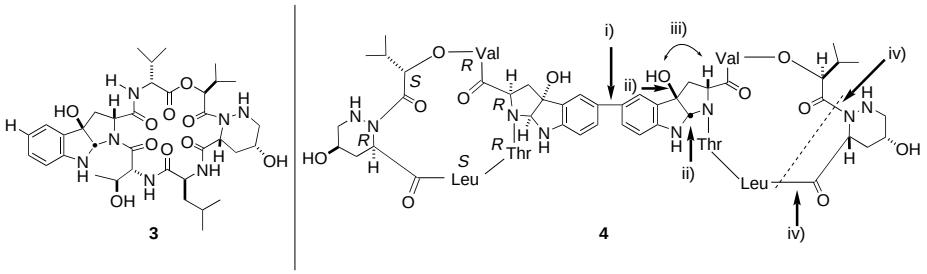

Figure 3. Key synthetic issues and potential bond disconnections.

monomer is apparently not available from fermentation or from degradation of himastatin, chemical synthesis would be required for such a study.

Broadly speaking, one could anticipate several key issues which would require particularly close attention in attempting a total synthesis of himastatin. In citing these problem areas, we imply no a priori commitment as to the sequence in which they would be addressed. Clearly, there is a need, at some stage, to achieve coupling of the indole moieties (see arrow i) in structure **4**, Figure 3). Another potentially serious impediment could be the building of the pyrroloindoline with the angular hydroxyl group at C3a ii). It would be necessary to correlate the stereochemistry of the *cis* pyrrolo[2,3-b]indoline with the acyl function of the modified tryptophan, Figure 3 iii). Workable routes to the amino acids or amino acid surrogates which are to be interpolated between the "tryptophyl" carboxy and N_b functions would be required. A particularly novel segment of the five-component insert needed to establish the depsipeptide, is the rather rare 5-hydroxypiperazic acid in the D-amino acid configuration (Figure 3 iv).[6] Needless to say, the subtleties of protecting these building blocks as they are entered into the evolving depsipeptide domain must be mastered. Moreover, creation of a setting for successful deprotection of the various subunits without unraveling fragile functional group accommodations would pose no small challenge to the enterprise.

Synthesis of *anti–cis* (11) and *syn–cis* (14) pyrroloindoline cores: With the potential difficulties well appreciated, we initiated our quest by focusing on the pyrroloindoline problem. Even confining our inquiry to the *cis* [2,3-b] series and setting aside considerations of absolute configuration, it would be necessary to achieve decent control in setting the relation of this fusion relative to the acyl (carboxamido) center of the modified tryptophyl subunit. Put differently, if we would commence with a suitably protected tryptophan **5**, shown in the D-configuration, it would be necessary to gain access to the *anti–cis* series (cf. **7**) corresponding to the assigned structure of himastatin (Figure 4). Ideally, at least for purposes of molecular diversification, it could be helpful if we could also gain stereoselective access to the *syn–cis* series (cf. **6**). Indeed as matters unfolded (see below), this capability proved to be crucial.

The possibility of inducing oxidative cyclization of various tryptophan derivatives such as **5**, followed by aromatization (loss of HX) which led to **8**, had been appreciated since the pioneering work of Witkop (Figure 5).[7] Our first thought was

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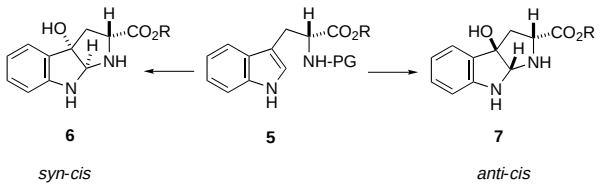


Figure 4. Oxidative cyclization of tryptophan.

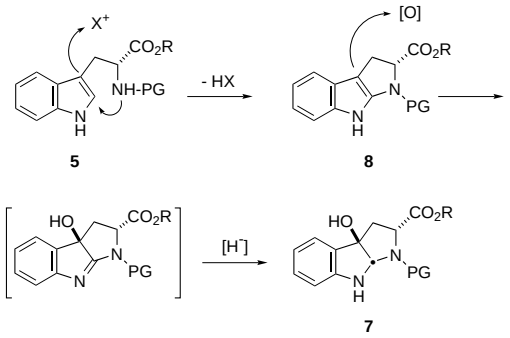
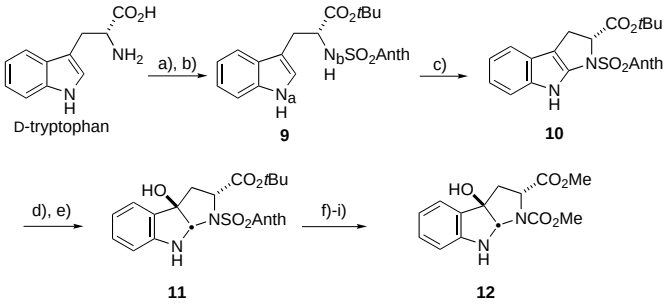


Figure 5. Witkop's oxidative transposition of tryptophan.

to accomplish the required conversion through a substrate that yields a product which can be hydrated (by oxidation followed by reduction) with high stereoselection in the *anti–cis* sense, to reach a system of type **7**. To bring this result about, the N_b nitrogen of the tryptophan had to be subject to deprotection of its blocking group with maintenance of the aromatic "hydrate" substructure. These stringent criteria were met through the use of the anthracene sulfonyl protecting group as the N_b protecting group (PG),[8] while a *tert*-butyl ester (R) served to protect the carboxyl function (see compound **9**, Scheme 1). Treatment of **9** with NBS and

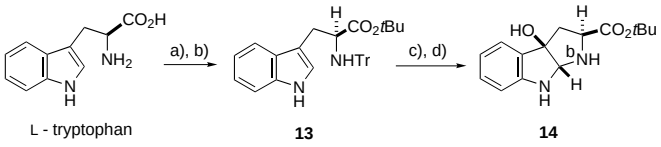


Scheme 1. Synthesis of pyrroloindoline **11**. a) $AnthSO_2Cl$, TEA, THF; b) *tert*-butyl isourea, CH_2Cl_2, rt, 70% (over two steps); c) NBS, TEA, CH_2Cl_2, 0 °C to rt; d) DMDO, CH_2Cl_2, −78 °C; e) $NaBH_4$, MeOH, 0 °C to rt, 75% (over three steps); f) TFA, CH_2Cl_2; g) CH_2N_2, Et_2O; h) Al(Hg), THF, aq NH_4OAc; i) $ClCO_2Me$, py, CH_2Cl_2, −78 °C to rt, 50% (over four steps).

triethylamine generated an unstable dihydropyrroloindole **10**. Subsequent treatment of this compound with 3,3-dimethyldioxirane (DMDO) at −78 °C followed by reduction with sodium borohydride led to **11** as substantially a single diastereomer. The use of a *tert*-butyl ester afforded a much higher *anti* to *syn* stereoselectivity (>15:1) in the oxidation step than the corresponding methyl ester which provided a more modest 3:1 preference. Interestingly, of the protecting groups PG, which were surveyed for N_b, only those of the sulfonyl type ($AnthSO_2$, SES, Ts) were appropriate for subsequent oxidation of the pyrroloindole tetrasubstituted double bond with DMDO. Other protecting groups at N_b (Boc, CO_2Me, Ac, Tr) and other oxidants (OsO_4, MCPBA, MMPP, $Pb(OAc)_4$) failed to give the desired products in useful yields.[9]

The anthracene sulfonyl residue had been chosen among the various sulfonyl groups because of the ease of its removal under mild reducing conditions (SmI_2, THF, rt, min, or Al(Hg), THF, H_20, rt, h). For additional verification, the transformation of **11** → **12** was also accomplished. The correlation of this compound with compounds previously assigned to be in the "*anti–cis*" series strongly supported our assignments.[10]

We next turned to the matter of gaining stereospecific access to the *syn–cis* pyrroloindoline series. At the time we undertook this study, the idea was to expand our options for diversifying himastatin congeners. We were mindful that this type of transformation had not been accomplished by direct cyclization of a tryptophan derivative with high stereoselectivity.[11] Many tryptophan-derived congeners were screened as to their amenability to stereospecific oxidative cyclization in the desired mode. After considerable trial and error type research, we found that the N_b-trityl substrate, as its *tert*-butyl ester (see compound **13** derived from L-tryptophan as shown), gave **14** in 55% yield upon oxidation with DMDO and cleavage of the trityl group apparently unaccompanied by any *anti–cis* diastereomer (Scheme 2).



Scheme 2. Synthesis of pyrroloindoline **14**. a) TrCl, TEA, THF; b) *tert*-butyl isourea, CH_2Cl_2, rt, 76% (over two steps); c) DMDO, CH_2Cl_2, −78 °C; d) HOAc, MeOH, CH_2Cl_2, 55% (over two steps).

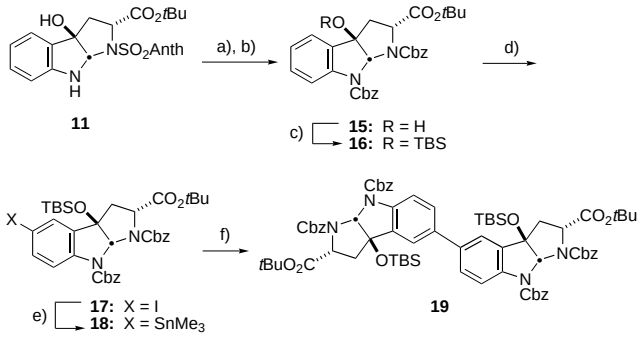
At this stage we had accomplished our key early objective of gaining smooth and highly stereoselective access to both the *anti–cis* and *syn–cis* versions of the [2,3-b]-pyrroloindole series. Our expectation was to use the former as a building block to obtain himastatin while the latter might be useful for SAR investigations.

Synthesis of dimer 24: Our focus then shifted to paving the way for the bi-aryl linkage (see i) in structure **4**, Figure 3). We were rather aware of the fact that if the biaryl linkage could be introduced at an early stage, the building of the depsipeptide could be conducted concurrently on the two identical subunits potentially with a notable economy of operations. We came to favor a Stille coupling for the biaryl bond formation.[12] This route was all the more interesting since it had not yet been reported in the bisindolyl series.

We had of course benefited from the availability of D-tryptophan to reach **11**. Now it would be necessary to functionalize the benzo region at the required carbon of the

indolenine. We reasoned that N_a, even if modified with a protecting group, might direct an electrophilic functionalizing agent to the C-5 position.

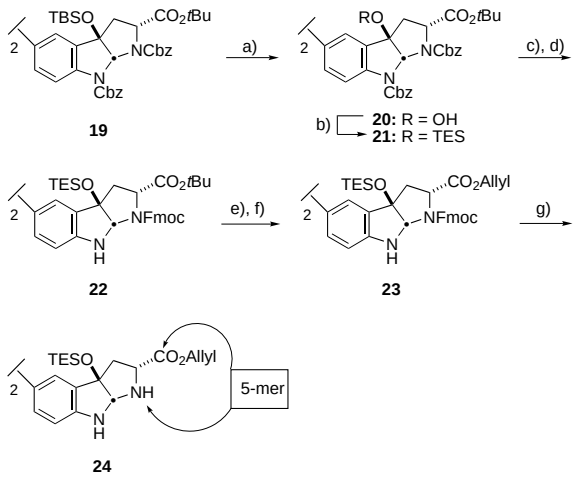
Much trial and error was required before N_a as well as N_b were presented in an optimal way for accomplishing clean functionalization at the C-5. In practice compound **11** lent itself to conversion to **16** through a three-step sequence (Scheme 3). Protecting group interplay was required at this



Scheme 3. Synthesis of pyrroloindoline dimer **19**. a) Al(Hg), THF, aq NH_4OAc; b) CbzCl, py, CH_2Cl_2, rt, 60% (over two steps); c) TBSCl, DBU, DMF, 50°C, 77%; d) ICl, 2,6-di-*tert*-butylpyridine, CH_2Cl_2, 81%; e) Me_6Sn_2, $[Pd(Ph_3P)_4]$, THF, 60°C, 89%; f) $[Pd_2dba_3]$, Ph_3As, **17**, DMF, 45°C, 50–70%.

point since neither the anthracene sulfonyl group nor the free NH or OH functions were compatible with the iodination conditions. With the particular set of protecting groups shown, iodination at C-5 of the indoline occurred as indicated (see compound **17**). The stannyl indole **18** was prepared from **17** as shown. Happily and seemingly uneventfully, a palladium mediated Stille coupling of **17** and **18** gave rise to **19**. The critical campaign for a two-fold interpolation of the depsipeptide between N_b and the tryptophan derived carboxy center could now commence.

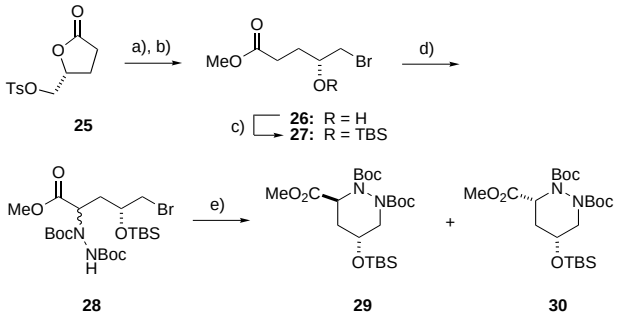
Significant restructuring of this pyrroloindoline domain was necessary to render it suitable for initial attachment to the depsipeptide domain, as well as for macrocyclization and ultimate deprotection (Scheme 4). For instance, parallel studies in related series suggested that we would not be able to deprotect an angular TBS group at C-3a when the *full* macrocycle was in place. Hence, the TBS protecting group was cleaved at the stage of **19**. Fortunately, a triethylsilyl function could be introduced at this point through the use of TESCl in the presence of DBU to provide **21**. Additionally, on the basis of model probe studies, it appeared that reliance of a *tert*-butyl ester for carboxy protection would lead to difficulties in late stage deprotection. Accordingly, we replaced this group with an allyl ester which could be cleaved through palladium mediated π-allyl formation at a strategic point of our choosing. Of course, the presence of an allyl group from the start would not have been compatible with our oxidative cyclization. The four Cbz functions were discharged under standard hydrogenation conditions and the resulting tetraamine was reprotected as its bis-Fmoc derivative (see compound **22**). The *tert*-butyl ester function was cleaved with triethylsilyltriflate and 2,6-lutidine. Hydrolysis of the resultant



Scheme 4. Synthesis of pyrroloindoline dimer **24**. a) TBAF, THF, 85%; b) TESCl, DBU, DMF, 50°C, 79%; c) H_2 (1 atm), Pd/C, EtOAc; d) Fmoc-HOSu, py, CH_2Cl_2, 87% (over two steps); e) TESOTf, lutidine, 0°C to rt, CH_2Cl_2; f) allyl alcohol, EDCI, DMAP, CH_2Cl_2, 78% (over two steps); g) piperidine, CH_3CN, 92%.

triethylsilyl esters and reprotection of the diacid as its bis-allyl ester afforded derivative **23**. Finally, the Fmoc functions were cleaved upon reaction of **23** with piperidine, thereby providing access to **24**. In relying on the doubly deprotected diamine arrangement (N_b and N_a), we expected that N_b would be more reactive than the "aniline-like" N_a.

Synthesis of piperazic acid 32: Our next subgoals involved gaining access to the five building blocks comprising the depsipeptide. The individual units would be pre-assembled to produce the 5-mer which would be interpolated between N_b and the erstwhile tryptophan carboxyl function. Even casual inspection of these subunits forecasts that the most complex of them would be the 5-hydroxypiperazic acid moiety, properly presented for incorporation into the 5-mer. The synthesis had to be responsive to the relative and absolute stereochemistry required for himastatin. This subgoal was accomplished through two different schemes.[13] In the first (Scheme 5), methanolysis of commercially available tosylate **25** at rt gave an epoxy ester. The oxido linkage suffered opening with LiBr and HOAc, which gave hydroxy ester **26**. Protection of the resulting secondary alcohol as its *tert*-



Scheme 5. Synthesis of piperazic esters **29** and **30**. a) NaOMe, MeOH, 0°C to rt; b) LiBr, THF, HOAc, rt, 93% (over two steps); c) TBSOTf, lutidine, CH_2Cl_2, –78°C to rt, 65%; d) NaHMDS, THF, DBAD, –78°C to rt, 79%; e) NaH, DMF, 0°C, 44% of **29**, 37% of **30**.

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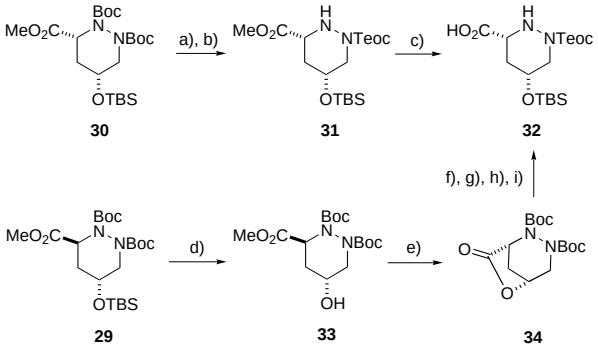
butyldimethylsilyl ether led to **27** in good overall yield for the three steps. Deprotonation with strong base (NaHMDS) followed by quenching with bis-Boc azodicarboxylate afforded **28** as a roughly 1:1 mixture of diastereomers. Exposure of this mixture to NaH in DMF at 0 °C led to smooth cyclization giving piperazic esters **29** and **30** after a difficult separation.

The *cis*-ester **30** was advanced to **32** through ester **31** in a straightforward manner as shown (Scheme 6). Much effort was expended to make use of the undesired *trans* piperazic ester **29** by means of epimerization. Success was ultimately

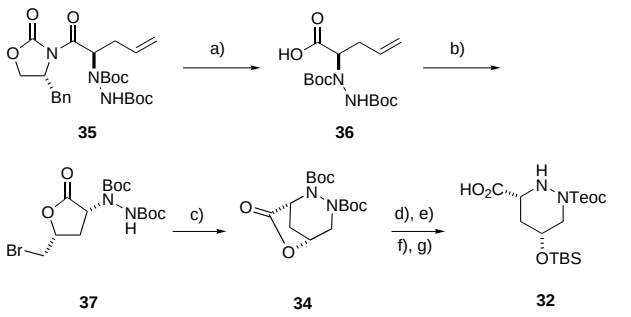


Scheme 6. Synthesis of piperazic acid **32**. a) TFA, CH_2Cl_2; b) TeocCl, iPr$_2$NEt, CH_2Cl_2, 92% (over two steps); c) LiOH, THF, 0 °C, 100%; d) TBAF, THF, 0 °C to rt, 80%; e) DBU, toluene, 110 °C, 69%; f) TFA, CH_2Cl_2; MeOH; g) TeocCl, py, CH_2Cl_2; h) TBSOTf, lutidine, CH_2Cl_2, −78 °C to rt; i) LiOH, THF, 0 °C, 82% (over four steps).

accomplished as seen in Scheme 6. TBAF deprotection of **29** cleanly gave secondary alcohol **33** in 80% yield. Refluxing this *trans*-hydroxy ester with DBU in toluene using a Dean–Stark trap filled with 4 Å molecular sieves led to a slow, but clean conversion to the *cis* piperazic lactone **34**. Acidic cleavage of both Boc functions, and methanolysis of the lactone, acylation of the remote nitrogen with TeocCl, silylation of the alcohol function, and ester hydrolysis led to **32**. In theory, a mixture of *cis* and *trans* esters (**29** and **30**) could be taken on through this sequence thereby obviating the need for a difficult chromatographic separation. Albeit less than elegant from the standpoint of stereocontrol, the approach is amenable to scale-up and requires a minimal number of purification steps.

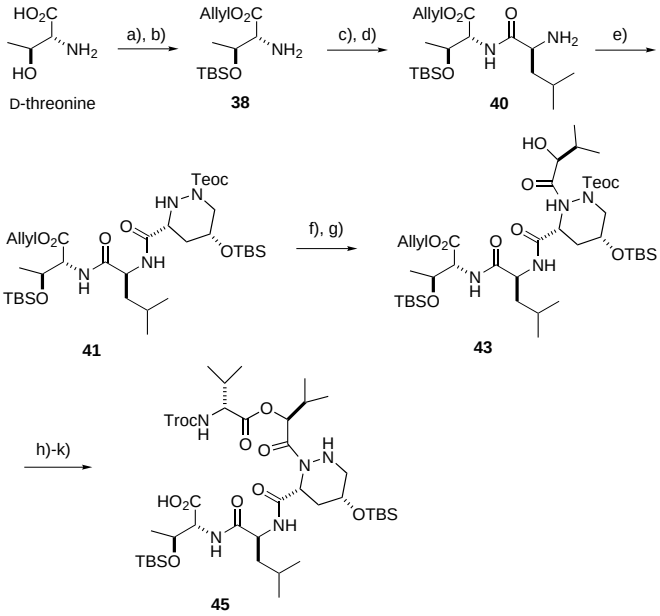
A second generation, stereoselective approach to the piperazic acid was also developed. The route started with the known pentenoic acid derivative, **35** (Scheme 7).[14] Cleavage of the acyl oxazolidinone bond was accomplished through lithium hydroxide in THF. Bromolactonization of the resulting acid **36** under the influence of *N*-bromosuccinimide gave a ≈4.5:1 ratio of **37** relative to its *trans* counterpart.[15, 16] The bromine function was displaced upon deprotonation of the second Boc nitrogen giving rise to lactone **34**. As before, four straightforward steps converted **34** into acid **32**.

Pentadepsipeptide synthesis: The other four fragments which were employed in building the peptidal domain were: i) the D-threonine derivative **38**, ii) Fmoc-L-leucine **39**, iii) the hydroxyisovaleryl derivative **42** (prepared from commercially available (*S*)-hydroxyisovaleric acid), and iv) D-valine, as its



Scheme 7. Alternate synthesis of piperazic acid **32**. a) LiOH, THF, 0 °C, 71%; b) NBS, toluene, 0 °C, 65%; c) NaHMDS, DMF, 0 °C, 64%; d) TFA, MeOH; e) TeocCl, py, CH_2Cl_2; f) TBSOTf, lutidine, CH_2Cl_2, −78 °C to rt; g) LiOH, THF, 0 °C, 82% (over four steps).

Troc derivative **44** (Scheme 8). Of these, **39** is commercially available. The remaining components **38**, **42**, and **44** were all derived from well established chemistry.

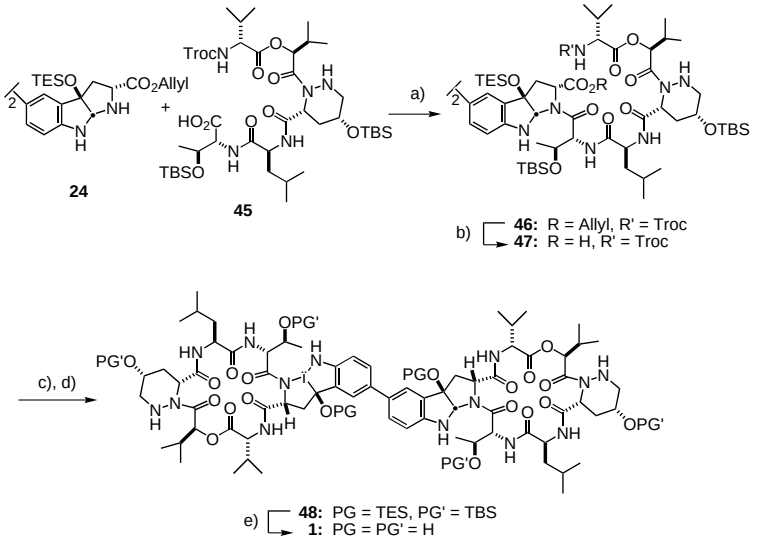


Scheme 8. Synthesis of pentadepsipeptide acid **45**. a) allyl alcohol, *p*-TsOH, C_6H_6, Dean-Stark, 80 °C; b) TBSCl, imidazole, CH_2Cl_2, 99% (over two steps); c) Fmoc-L-leucine (**39**), EDCI, DMAP, CH_2Cl_2; d) piperidine, CH_3CN, 88% (over two steps); e) piperazic acid (**32**), HATU, HOAt, collidine, CH_2Cl_2, 70–95%; f) Fmoc-OCH(*i*Pr)COCl (**42**), collidine, CH_2Cl_2, 0 °C to rt; g) piperidine, CH_3CN, 92% (over two steps); h) Troc-D-valine (**44**), IPCC, Et_3N, DMAP, CH_2Cl_2, −20 °C to rt; i) $ZnCl_2$, CH_3NO_2; j) TBSOTf, lutidine, CH_2Cl_2, −78 °C to rt; k) [Pd(Ph$_3$P)$_4$], PhSiH$_3$, THF, 0 °C to rt, 69% (over four steps).

With the requisite building blocks in hand, assembly of the 5-mer domain could commence. Coupling of **38** with **39** was followed by cleavage of the Fmoc group to release the leucine amino function (see compound **40**). The latter was acylated with the piperazic acid **32**, to provide tripeptide **41**. Fortunately, the relatively unreactive NH moiety of the piperazic acid **41** was subjected to acylation by **42**. Following deprotection, building block **43** was in hand. Acylation of **43** with **44**, deprotection of the three silyl groups, reprotection of the diol, and deprotection of the allyl ester gave the required acid **45**.

This sequence was required since projected removal of the Teoc group on the piperazic fragment was highly problematic in the context of the full himastatin core structure. Hence, this deprotection had to precede incorporation of the 5-mer into the sensitive himastatin architecture. Fortunately, the free piperazic NH group in **45** is relatively unreactive. With careful management of reaction conditions, it proved to be possible to carry this NH group forward into the synthesis.

Synthesis of dimer 1 and monomer 3: The next stage of the venture would involve interpolation of the 5-mer, now identified as **45**, between N_b and the acyl group of **24** (Scheme 9). We would be confronting the question of the differentiability of the two NH groups of **24**. We would, at every stage, be testing the stability of the pyrroloindoline moiety, bearing the angular silyl protected tertiary alcohol and, as discussed above, the accomodatability of the free NH group of the piperazic acid. Subunit **45** would be presented as the deprotected carboxyl in the threonine residue. The valine amino terminus is protected as a Troc-urethane. Correspondingly, in **24**, the tryptophan derived carboxyl of the pyrroloindole sector is protected as an allyl ester, leaving N_a and N_b as free NH groups to potentially compete for acylation by the threonine carboxyl function. As noted earlier, we hoped that the "aniline-like" N_a would be less reactive than N_b.



Scheme 9. Synthesis of isohimastatin **1**. a) HATU, HOAt, collidine, CH_2Cl_2, $-10\,^{\circ}C$ to rt, 67%; b) $[Pd(Ph_3P)_4]$, $PhSiH_3$, THF, $0\,^{\circ}C$ to rt, 86%; c) Pb/Cd couple, THF, aq NH_4OAc; d) HATU, HOAt, iPr_2NEt, DMF, $0\,^{\circ}C$ to rt; e) TBAF, HOAc, THF, 48% (over three steps).

Fortunately, coupling of **24** with two units of **45** under the highly controlled conditions shown, occurred exclusively at the N_b centers giving rise to **46**. The next phase involved exposure of the trytophyl carboxyl group (from its allyl ester) and the valine amino group from its Troc derivative. These steps were accomplished in the manner shown. In the defining step of the synthesis, two-fold cyclization of the crude diamino acid led to the bis-macrolactam **48**. As discussed above, the ground work to enable the final deprotection had been carefully surveyed. In the event, concurrent deprotection of the angular pyrroloindoline hydroxyl (from its TES derivative) and the piperazic and threonine based hydroxyl groups (from their TBS ethers) was possible and the goal structure **1** was in hand.

The excitement at having ostensibly reached our synthesis end point was short lived. Unfortunately, it was clear that the ^1H NMR spectrum of the final product, prepared in our laboratory by the synthesis described above, did not correspond with that recorded for naturally derived himastatin,[2b,c] also *presumably* corresponding to **1**. Particularly striking were two upfield signals at $\delta = 0.55$ and 0.35 in synthetic **1**, attributable to the nonequivalent methyl centers in the valine isopropyl moiety. No such upfield resonances are present in the reported ^1H NMR spectrum of himastatin isolated from natural sources.

Additionally, the gross properties of the synthetic construct differed from those described for himastatin. Thus, the natural product was reported to be soluble in a variety of organic solvents (CH_2Cl_2, $CHCl_3$, EtOAc, MeOH) with an $t_R =$ 0.6 (8:1 $CHCl_3$/MeOH). Although soluble in DMSO, synthetic **1** is insoluble in CH_2Cl_2, $CHCl_3$, EtOAc, MeOH, and is much more polar with an $t_R =$ 0.15 (8:1 $CHCl_3$/MeOH).

Moreover, the synthetic logic to reach dimer **1** was applied to the synthesis of monomeric **3**. For this goal, we returned to compound **11** (Scheme 10). The *tert*-butyl group of the ester function was cleaved and an allyl ester was built. N_b was exposed by reductive cleavage (Al(Hg)) of the sulfonamide (see compound **50**). Coupling of **50** specifically at N_b with acid **45** led to *seco*-system **51**. The synthesis proceeded in much the same manner as that used to reach **1**. Once again, the ^1H NMR spectrum of this monomer **3** had upfield peaks at $\delta = 0.55$ and 0.35 which had no counterpart in the reported spectrum of himastatin.[2b,c]

Correction of stereochemistry: At this stage, two possible conclusions suggested themselves. It could be argued that during the course of our total synthesis, an unanticipated epimerization or even skeletal rearrangement had taken place. Upon carefully and critically reviewing our methodology and data, we came to regard this family of possibilities as most unlikely. This view led us to the next alternative, that is that the structure (possibly at the stereochemical level) of the "real" naturally occurring himastatin is not identical to that which had been assigned. Favoring this accounting for the mysterious non-congruence of synthetic end product and naturally derived material, we then directed our efforts

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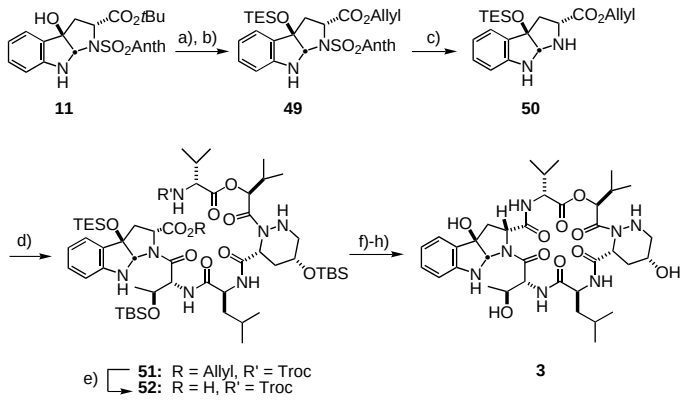
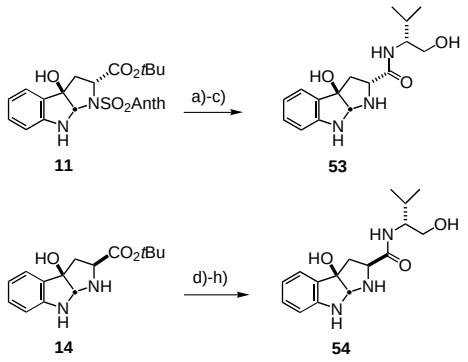


Scheme 10. Synthesis of *trans*-monomer **3**. a) TESOTf, *i*Pr_2NEt, CH_2Cl_2, 0 °C to rt; b) allyl alcohol, EDCI, DMAP, CH_2Cl_2, 78% (over two steps); c) Al(Hg), THF, H_2O, 69%; d) acid **45**, HATU, HOAt, collidine, CH_2Cl_2, −10 °C to rt, 66%; e) [$Pd(Ph_3P)_4$], $PhSiH_3$, THF, 0 °C to rt, 92%; f) Pb/Cd couple, THF, aq NH_4OAc; g) HATU, HOAt, *i*Pr_2NEt, DMF, 0 °C to rt; h) TBAF, HOAc, THF, 76% (over three steps).

toward ascertaining the nature of the discrepancy. For this purpose, we focused on opportunities suggested by the previously described degradation product, assigned to be **2**, containing the sensitive [2,3-b]-pyrroloindoline moiety as well as the D-valinol side chain. Since the ^{1}H NMR spectra of **1** and the monomeric **3** were virtually identical in the depsipeptide sector, we reasoned that a comparison of the high field spectra reported for the degradation product presumed to be **2** with a candidate monomeric version thereof, while imperfect in terms of intellectual rigor, would be revealing in practice. Hence, we returned to compound **11** (Scheme 11). It was



Scheme 11. Synthesis of degredation monomers **53** and **54**. a) TFA, CH_2Cl_2; b) D-valinol, EDCI, DMAP, CH_2Cl_2; c) Al(Hg), THF, H_2O, 25% (over three steps); d) Fmoc-HOSu, pyridine, CH_2Cl_2; e) TMSOTf, lutidine, CH_2Cl_2, 0 °C to rt; f) D-valinol, EDCI, DMAP, CH_2Cl_2; g) piperidine, CH_3CN; h) TFA, CH_2Cl_2, 28% (over five steps).

readily converted to **53** as shown. Once again, the chemical shift data for the isopropyl group in **53** ($\delta = 0.78$, 0.62) and those reported for **2** ($\delta = 0.94$ and 0.89) were not in accord. Hence, there was strong indication of a discrepancy between the relative configurations proposed for himastatin in the pyrroloindole valinol sector and the synthetically derived structure **53**, which we took to be secure.

Reflecting a growing suspicion as to the nature of the discrepancy between synthetic **1** and himastatin, we returned to the previously synthesized tryptophan derivative **14**. It will be recalled that this substance had been derived from L-tryptophan, but is in the *syn*–*cis* series. The methodology for converting **14** to the corresponding D-valinol derivative **54** was, in principle, well in hand, provided that the protocols which had been operative in the *anti*–*cis* series leading to **1** and **3** would now be transferable to the *syn*–*cis* regime. Indeed, this turned out to be the case and compound **54** was synthesized as shown. In this case, the key features of the high field ^{1}H NMR spectrum of the synthetic *syn*–*cis* "monomer" version of the bis-valinol degradation product matched the reported values for the dimer. Thus, the resonances of the nonequivalent isopropyl methyl groups of **54** are at $\delta = 0.92$ and 0.88; this matches closely the reported resonances at 0.94 and 0.89 of the degradation product previously reported to be **2**, but which in fact now would require re-formulation.

Further experimental evidence gleaned from the literature bears on the *anti*–*cis* versus *syn*–*cis* stereochemical issue. Both *trans* and *cis* esters **12** and **55** have been characterized by ^{1}H NMR and by X-ray crystallography (Figure 6).[10] In **12**, the methyl ester singlet appears at $\delta = 3.20$ while that in **55** is seen at $\delta = 3.80$. From the crystallographically derived structure of **12**, the methyl ester is clearly on the concave face of the tricycle and would be expected to experience the shielding effect of the aromatic ring. This chemical shift difference between the *trans* and *cis* esters follows the trend we were now proposing to extend to compounds **53** and **54**.

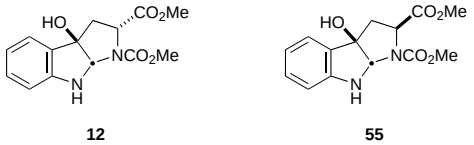


Figure 6. Structures of known relative stereochemistry confirmed by X-ray analysis.

On the basis of these findings and considerations, we were prepared to postulate that the relationship of the pyrroloindoline junction moieties and the tryptophane-carboxamido group in naturally occurring himastatin is *syn* rather than *anti* as previously proposed.

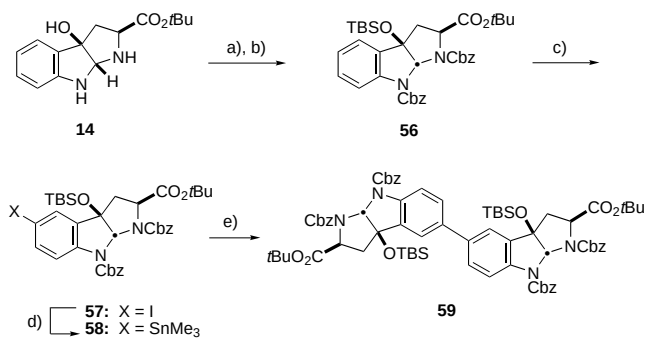
Having reached this stage in our reformulation of the structure of himastatin, there were still uncertainties. Of course, we could not be sure that the depsipeptide domain of the natural product had in fact been correctly formulated. Given the similarity of the high field ^{1}H NMR spectra of synthetic **1** with that described for himastatin (neglecting the difference in the methyl resonances in the isopropyl group) we started with the assumption that the depsipeptide sector of natural himastatin is as asserted. However, even if this is assumed to be the case, there was no evidence with which to formulate the absolute stereochemistry of the tryptophan derived pyrroloindoline. In principle, it could indeed be derived from D-tryptophan with the discrepancy rooted exclusively in the *syn* relationship of the *cis* junction to the carboxamido group. Alternatively, the tryptophan in question may be L-configured. In this event, the "absolute stereo-

chemistry" of the pyrroloindoline junction would have been correctly formulated. However, the L-carboxamido configuration would be *S* rather than the *R* in **1**, and its relationship to the junction functions, accordingly, would be *syn* rather than *anti*.

In evaluating the issue of assignment of the tryptophan derived (D or L) pyrroloindoline and the clear need to reverse the *anti–cis* assignment to a *syn–cis* arrangement, the chiroptical data cited in support of the original assignment is more readily accommodated in the context of an L-tryptophan derived insert. By reversing this configuration of the carboxamido group (D-tryptophyl → L-tryptophyl) the junction substituents of the pyrroloindoline would be the same as that originally proposed in **1**. We also noted with interest that if the pyrroloindoline were indeed derived from L-tryptophan and the 5-mer were indeed properly formulated, the components in the depsipeptide domain are presented in alternating D- and L-configurations. Recent studies by Ghadiri on the special properties associated with related systems might explain the markedly different solubility and polarities described above for himastatin and **1**.[17a, b, c]

Given these considerations we advanced the structure **68** for himastatin and **69** for its bis-valinol degradation product. We well recognized that our proposal was not secure. In addition to the unproven assignment of an L-tryptophan absolute configuration for the pyrroloindoline sector, we had no verification for supposing that the depsipeptide 5-mer region of himastatin would correspond in all its detail to that which had been assigned. Given the practicalities of our situation, wherein no significant quantities of himastatin were available, chemical synthesis emerged as the only means to solve the problem of the structure of himastatin in a rigorous fashion.

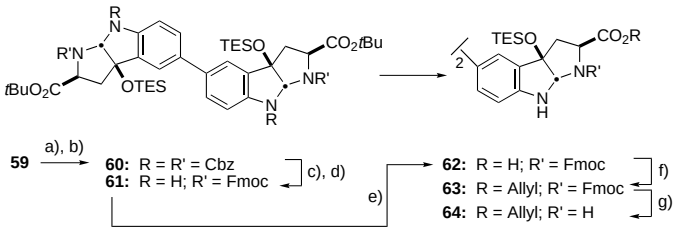
Synthesis of himastatin (68): Accordingly, we returned to L-tryptophan and to the previously described **14**, hoping that the methodology carefully developed in closely related models would prove to be adequate (Scheme 12). The protecting groups (of **14**) were re-organized in a fashion suggested by previous experiences. Cbz groups were introduced at N_a and N_b. The junction hydroxyl group was protected as its TBS ether (see compound **56**). We were now poised to undertake the oxidative dimerization of a suitably presented monomer.



Scheme 12. Synthesis of pyrroloindoline dimer **59**. a) CbzCl, py, CH_2Cl_2; b) TBSCl, DBU, DMF, rt, 61% (over two steps); c) ICl, 2,6-di-*tert*-butylpyridine, CH_2Cl_2, 73%; d) Me_6Sn_2, [$Pd(Ph_3P)_4$], THF, 60°C, 87%; e) [Pd_2dba_3], Ph_3As, **57**, DMF, 45°C, 83%.

In the event, upon reaction of **56** with ICl, an iodine atom was introduced at C-5 (see compound **57**). A portion of **57** was converted to aryl stannane **58** as shown. At this stage, we could hope to take advantage of precedent, demonstrated in the *anti–cis* series, to join sophisticated pyrroloindolines in their "benzo" sectors through carbon to carbon bond formation by an extension of the Stille reaction. In the event compounds **57** and **58** did couple smoothly under the conditions shown to produce **59**.

Once again, a restructuring of the protecting groups was required to facilitate interpolation of the 5-mer and to anticipate the sensitivity associated with global deprotection in the last step. The protocols which we employed to convert the *trans*-dimer **19** to a suitable coupling partner (i.e., **24**) were equally successful in the *syn–cis* series (see **59** → **64**, Scheme 13). Thus, cleavage of the angular TBS group exposed the angular alcohol which was quickly reprotected as its



Scheme 13. Synthesis of pyrroloindoline dimer **64**. a) TBAF, THF; b) TESCl, DBU, DMF, 95% (over two steps); c) H_2 (1 atm), Pd/C, EtOAc; d) Fmoc-HOSu, py, CH_2Cl_2, 96% (over two steps); e) TESOTf, lutidine, CH_2Cl_2, 0°C to rt; f) allyl alcohol, DBAD, Ph_3P, THF, 81% (over two steps); g) piperidine, CH_3CN, 74%.

triethylsilyl derivative **60**. The two Cbz functions were cleaved by hydrogenolysis and two Fmoc groups (one per domain) were introduced at N_b (see compound **61**). The moment was in hand for cleaving the *tert*-butyl ester so that it could be replaced by an allyl ester function in turn poised for a highly specific deprotection under mild conditions at a strategic point of our choosing. This subgoal was accomplished by treatment of compound **61** with TES triflate, as shown, resulting in exposure of the free "tryptophyl-like" carboxylic acid **62** in each component of the dimer. Each acid was converted to its allyl ester as indicated (see compound **63**). There remained only the cleavage of the Fmoc group to allow for presentation of the pyrroloindoline in a form which could be acylated by the threonine carboxyl of the previously encountered **45**. The Fmoc groups, protecting the two identical N_b functions, were readily cleaved providing compound **64** for presentation to 5-mer **45**.

Fortunately, acylation occurred smoothly at both N_b functions in **64** with the threonine derived carboxyl in **45** providing a 60% yield of **65** (see Scheme 14). We were now well positioned to take advantage of the highly specific deprotection of the two allyl esters of the identical pyrroloindoline sectors (see compound **66**). Once again, cleavage of the two identical Troc groups served to expose the free amino groups of the valine residues. Fortunately, the resultant diamino acid underwent macrolactamization mediated by HATU to give rise to the lactam ester **67**. There remained the

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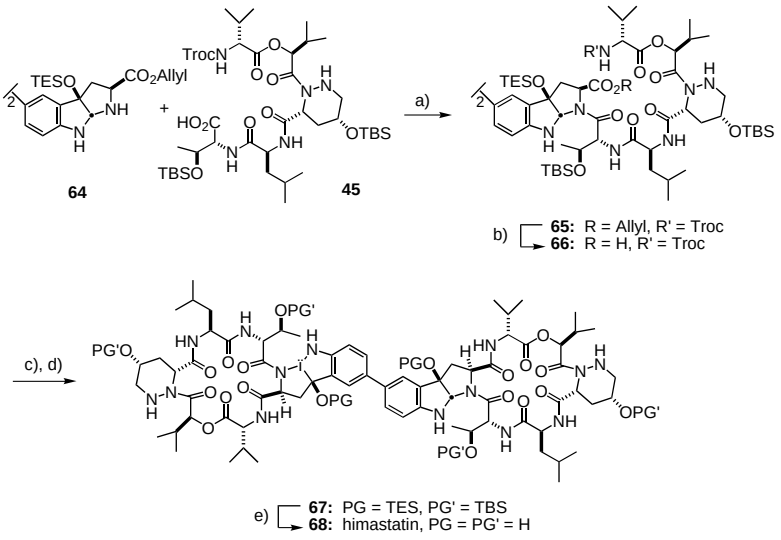


Scheme 14. Synthesis of himastatin **68**. a) HATU, HOAt, collidine, CH_2Cl_2, $-10\,^{\circ}C$ to rt, 60%; b) $[Pd(Ph_3P)_4]$, $PhSiH_3$, THF, $0\,^{\circ}C$ to rt, 81%; c) Pb/Cd couple, THF, aq NH_4OAc; d) HATU, HOAt, $i Pr_2NEt$, DMF, $0\,^{\circ}C$ to rt; e) TBAF, HOAc, THF, 34% (over three steps).

otherwise nontrivial matter of exposing the six hydroxyl groups of the final target. It was for the purpose of paving the way for such a step that we had taken the pains to introduce a TES group to protect the two equivalent hydroxyl functions at C-3a. Indeed, it proved possible to cleave the six silyl groups thereby providing **68**.

Happily, the high field proton spectrum of the fully synthetic himastatin (**68**) was identical with that published for the natural product. Thus encouraged, we obtained from the Bristol Myers group, a small amount of natural himastatin. We measured the 500 MHz ^1H NMR spectra of our fully synthetic material (which we thought to be **68**) along side that of the reference sample. It was clear by an overlay of these richly detailed spectra that the total synthesis of himastatin had been accomplished and that its structure is indeed **68**. The bis-valinol degradation product is therefore **69** (Figure 7).

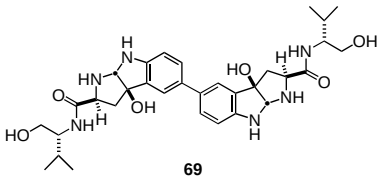
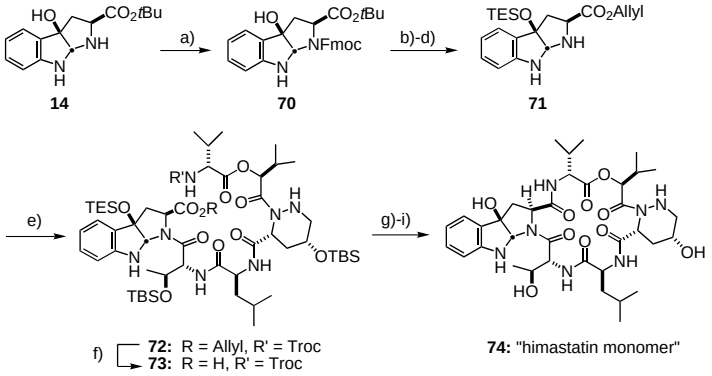


Figure 7. Corrected structure for himastatin degradation product.

In anticipation of comparative measurements of antibiotic activity in the himastatin series, we directed our attention to the synthesis of **74**, the "monomeric" version of himastatin. The methodology to synthesize this compound was by now well in hand. For this purpose we returned to compound **14** (Scheme 15). Selective Fmoc urethane formation occurred at N_b (see compound **70**). Protection of the angular hydroxy group was followed by deprotection of the *tert*-butyl ester and reprotection of the carboxyl group as an allyl ester. Ready discharge of the Fmoc group led to **71**, which was acylated with **45** (see compound **72**). Cleavage of the allyl ester gave **73** and, thence the *N*-Troc function afforded the *seco* acid. Macrolactamization followed by deprotection provided "himastatin monomer" **74**.

An evaluation of the antibiotic properties of four compounds: himastatin (**68**), isohimastatin (**1**) (originally proposed to be himastatin), *anti*-monomer **3** and *syn*-monomer **74** was undertaken.[18] A variety of microorganisms were screened. Indeed, himastatin (**68**) as reported strongly inhibited the growth of Gram-Positive bacteria such as *Enterococci faecalis*, whereas isohimastatin (**1**) was inactive.

We then evaluated monomer compounds **3** and **74**. It was found that **3**, which corresponds



Scheme 15. Synthesis of *cis*-monomer **74**. a) Fmoc-HOSu, py, CH_2Cl_2, 55%; b) TESOTf, lutidine, CH_2Cl_2, $0\,^{\circ}C$ to rt; c) allyl alcohol, DBAD, Ph_3P, THF; d) piperidine, CH_3CN, 46% (over three steps); e) acid **45**, HATU, HOAt, collidine, CH_2Cl_2, $-10\,^{\circ}C$ to rt, 52%; f) $[Pd(Ph_3P)_4]$, $PhSiH_3$, THF, $0\,^{\circ}C$ to rt, 92%; g) Pb/Cd couple, THF, aq NH_4OAc; h) HATU, HOAt, $i Pr_2NEt$, DMF, $0\,^{\circ}C$ to rt; i) TBAF, HOAc, THF, 78% (over three steps).

to the monomer version of isohimastatin (**1**), and **74**, which corresponds to the monomer version of himastatin (**68**), were both inactive when tested against a variety of Gram-Positive bacteria. Thus, both the "monomer" **3** and dimer **1**, in the *anti* series based on D-tryptophan and himastatin monomer (**74**) in the *syn* series based on L-tryptophan are all inactive. The role of the special topographic features of the alternating D and L subunits in the 6-mer depsipeptide remains to be established.[17]

It is also well to note that our findings in both the chemistry and biology of himastatin accord well with the very recent discovery of Umezawa in connection with the novel antibiotic chloptosin subsequent to our disclosures on himastatin.[19] Chloptosin (see Figure 8), like himastatin, is a potent antibiotic against Gram-Positive strains. It, too, contains a biaryl linkage (now with *ortho–ortho*' chlorine substituents). As in

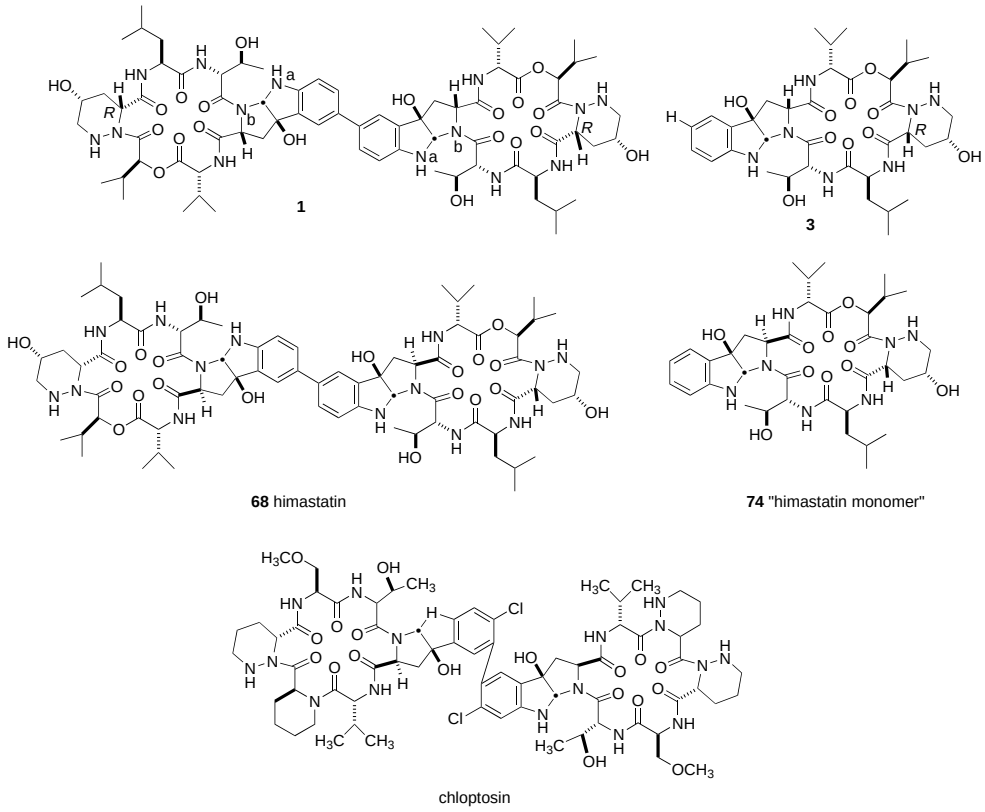


Figure 8. Structures of isohimastatin **1**, *trans*-monomer **3**, himastatin **68**, *cis*-monomer **74**, and chloptosin.

himastatin, there is a *syn*–*cis* pyrroloindoline motif as part of a hexapeptide ensemble. Once again, the hexapeptide (including two oppositely configured piperazic acids) is arranged with alternating D and L components. Hence, chloptosin partakes of those structural features of himastatin which we believe are critical to its function.

Conclusion

In retrospect, we had underestimated the scope and complexity of the himastatin problem. As matters transpired, chemical synthesis was able to demonstrate that the structure initially proposed for himastatin (i.e., **1**) was correct, except for the absolute configuration of the tryptophyl carboxamido center and its relationship to the *cis*-fused [2,3-b]-pyrolloindoline substructure. We now refer to compound **1** as "isohimastatin." Furthermore, the correct structure of naturally occurring himastatin was shown to be **68** and its degradation product retaining a single valinol unit per monomer domain is **69**.

In addition, through the medium of total synthesis, the outlines of a biological pharmacophore have been sketched out. It is critical to maintain the stereochemistry of himastatin in the pyrroloindoline–depsipeptide sphere. The cyclic depsipeptide of the active himastatin is characterized by alternating D- and L subunits in the "6-mer." Moreover, it was found that the presence of a biaryl arrangement with a C–C bond connecting the identical subunits is also necessary for biological activity. Thus "isohimastatin" (**1**), as well as isohimastatin monomer (**3**), are virtually inactive. More surprising was the finding that the *syn*-monomer **74**, corresponding in detail to the himastatin on all of its stereochemical relationships, is inactive.

For the moment, we assume that antibiotic properties of himastatin follow closely from the particular alternating D- and L substituents in the 6-mer and are contingent on the bidomainal motif. This pattern is simulated in a new antibiotic chloptosin and suggests a possible structural trend for orienting future SAR experiments.

At the chemical level, the synthesis provided a framework for solving the issue of achieving smooth stereospecific access to both the *anti*:*cis* and *syn*:*cis* pyrroloindoline subunits. The himastatin problem also brought with it the challenge of practical syntheses of 5-hydroxypiperazic acids in enantiomerically pure form. While improvements in terms of the stereoselectivity of our synthesis these piperazic acids can easily be imagined, the optically pure compounds are now accessible in multigram scale. Finally, it was necessary to sort out the optimal protecting group arrangements for facilitating orderly synthesis of himastatin including definition of conditions for enabling global deprotection. We are confident that the lessons learned from himstatin will transcend the hard won successful total synthesis shown here. Indeed, we expect that the methodology employed in reaching himastatin and "isohimastatin" will find broad application in the field of biologically active, structurally complex depsipeptides. It can well be argued that the himastatin problem is indeed illustrative of the discovery dimension of the science of total synthesis.

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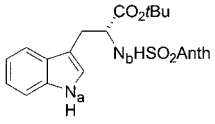
Experimental Section

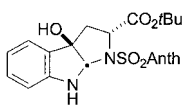
General methods: All reactions were run under an atmosphere of N_2 or argon and concentrations were performed under reduced pressure with a Büchi rotary evaporator, unless stated otherwise. Tetrahydrofuran (THF), Et_2O, and CH_2Cl_2 were degassed with argon and then passed through 4 × 36 inch columns of anhydrous neutral A-2 alumina (8 × 14 mesh; LaRoche Chemicals, activated under a flow of argon at 350 °C for 3 h) to remove H_2O. Toluene was degassed with argon and then passed through one 4 × 36 inch column of Q-5 reactant (Englehard; activated under a flow of 5% hydrogen/nitrogen at 250 °C for 3 h) to remove O_2 then through one 4 × 36 inch column of anhydrous alumina to remove H_2O. Triethylamine (Et_3N), hexane, pyridine, and diisopropyethyllamine (iPr_2NEt) were distilled from CaH_2 at atmospheric pressure. Reagents were purchased from Aldrich Chemical Company unless noted otherwise.

Instrumentation and chromatography: 400 MHz ^{1}H NMR and 125 MHz ^{13}C NMR spectra were measured on a Bruker QE 400 FT NMR. ^{1}H NMR chemical shifts are reported as δ values in ppm. ^{1}H NMR coupling constants are reported in Hz and refer to apparent multiplicities and not true coupling constants. Multiplicity is indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), appd (apparent doublet), appt (apparent triplet), dd (doublet of doublets); brs (broad singlet), etc. Mass spectra were measured on a Perkin–Elmer Sciex Model API-100 spectrometer with electrospray. TLC and column chromatographies were done with E. Merck silica gel. Acronyms: MMPP = Magnesium monoperoxyphthalate hexahydrate, HATU = *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate, HOAt = 1-hydroxy-7-azabenzotriazole, EDCI = 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, DMDO = 3,3-dimethyldioxirane, DBAD = di-*tert*-butyl azodicarboxylate, IPCC = isopropenyl chloroformate, NBS = *N*-bromosuccinimide, Cbz = benzyloxycarbonyl, dba = 1,5-dibenzylideneacetone, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, Fmoc = (9*H*-fluoren-9-ylmethoxy)carbonyl, HOSu = *N*-hydroxysuccinimide; TBAF = tetrabutylammonium fluoride; TBS = *tert*-butyldimethylsilyl, TES = triethylsilyl, Tf = trifluoromethylsulfonyl, Tr = triphenylmethyl, Teoc = 2-(trimethylsilyl)ethyloxycarbonyl, TFA = trifluoroacetic acid, HMDS = hexamethyldisilazane, Troc = (2,2,2-trichloroethoxy)carbonyl.

N_b-Anthracenesulfonyltryptophan *tert*-butyl ester (9): A solution of anthracenesulfonyl chloride (8.00 g, 29.0 mmol) in THF (50 mL) was added to a 0 °C solution of D-tryptophan (5.00 g, 24.2 mmol), Et_3N (10.0 mL, 72.5 mmol) and THF/H_2O (2:1, 300 mL). After 4 h, the mixture was diluted with EtOAc (100 mL) and acidified with aqueous 1M HCl until pH ≈3.0. The layers were separated and the aqueous layer was extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with aqueous 1M HCl (2 × 50 mL), brine (1 × 50 mL), dried (Na_2SO_4), and concentrated to give the crude acid as a yellow oil.



A mixture of the crude acid, *N*,*N*′-diisopropyl-*O*-*tert*-butylisourea (19.6 g, 98.0 mmol) and CH_2Cl_2 (100 mL) was aged at rt for 36 h. The solids were removed by filtration (Et_2O) and the filtrate was concentrated. This crude residue was purified by chromatography on silica gel (3:1 hexanes/Et_2O then 1:1 hexanes/Et_2O then 3:1 Et_2O/hexanes) to give **9** (8.60 g, 70%) as a pale yellow solid that was homogeneous by TLC analysis: m.p. 166–168 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.21 (d, J = 9.2 Hz, 2H), 8.45 (s, 1H), 7.92 (s, 1H), 7.86 (d, J = 8.3 Hz, 2H), 7.60–7.55 (m, 2H), 7.45–7.40 (m, 2H), 7.20 (d, J = 7.9 Hz, 1H), 7.10 (d, J = 8.1 Hz, 1H), 7.03 (t, J = 7.4 Hz, 1H), 6.88 (d, J = 2.1 Hz, 1H), 6.85 (t, J = 7.2 Hz, 1H), 5.81 (d, J = 8.0 Hz, 1H), 4.25–4.18 (m, 1H), 3.07 (dd, J = 14.7, 5.6 Hz, 1H), 2.98 (dd, J = 14.7, 7.0 Hz, 1H), 0.98 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.2, 135.6, 130.8, 130.1, 129.2, 128.6, 128.5, 126.7, 125.0, 124.6, 123.1, 121.6, 119.0, 118.0, 111.0, 108.8, 82.0, 56.5, 28.9, 27.2; IR (film): $\tilde{\nu}$ = 3477, 3019, 1728, 1399, 1215, 1149 cm^{-1}; ES-MS: *m*/*z*: calcd for $C_{29}H_{28}N_2O_4SNa$ $[M+Na]^+$: 523.17, found: 523.2; $[\alpha]_D^{25}$ = +10.5 (c = 1.0 in $CHCl_3$).

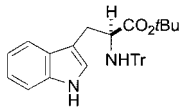


N_b-Anthracenesulfonylpyrroloindoline *tert*-butyl ester (11): Solid NBS (2.84 g, 16.0 mmol) was added to a 0 °C solution of **9** (8.00 g, 16.0 mmol) and CH_2Cl_2 (1 L). After 1 min, Et_3N (6.70 mL, 47.9 mmol) was added. The resulting orange solution was maintained at 0 °C for 30 min and then concentrated. The resulting residue was quickly purified by chromatography on silica gel (3:1 hexanes/Et_2O then 1:1 hexanes/Et_2O then 3:1 Et_2O/hexanes) to give **10** as an orange-red solid which was used without further purification.

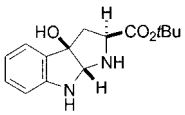
A solution of DMDO (≈0.08M in acetone, 200 mL, 16.0 mmol) was added in one portion to a −78 °C solution of this orange-red solid and CH_2Cl_2 (100 mL). The resulting pale yellow solution was aged at −78 °C for 10 min and then concentrated. $NaBH_4$ (1.80 g, 47.9 mmol) was added to a 0 °C solution of this crude residue and MeOH (100 mL). The resulting solution was allowed to warm to rt over ≈4 h and then was diluted with EtOAc (300 mL) and quenched with 1M HCl (100 mL). The layers were separated and the organic layer was washed with 1M HCl (3 × 100 mL), brine (2 × 100 mL), dried ($MgSO_4$), and concentrated to give **11** (8.00 g, 97%) as a pale yellow solid that was used without further purification.

A small portion of this solid was purified for analysis by chromatography on silica gel (3:1 hexanes/Et_2O then 1:1 hexanes/Et_2O then 3:1 Et_2O/hexanes then Et_2O) to give a light yellow solid that was homogeneous by TLC analysis: m.p. 188–191 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.31 (d, J = 9.3 Hz, 2H), 8.64 (s, 1H), 7.98 (d, J = 8.4 Hz, 2H), 7.68–7.60 (m, 2H), 7.50–7.42 (m, 2H), 7.09 (d, J = 7.7 Hz, 1H), 7.04 (t, J = 7.7 Hz, 1H), 6.67 (t, J = 7.4 Hz, 1H), 6.50 (d, J = 7.9 Hz, 1H), 5.08 (s, 1H), 4.81 (d, J = 8.8 Hz, 1H), 2.66 (d, J = 12.8 Hz, 1H), 2.56 (dd, J = 12.8, 9.3 Hz, 1H), 0.86 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.2, 149.6, 136.4, 131.1, 131.0, 130.7, 129.4, 128.9, 128.5, 127.8, 125.2, 124.8, 123.8, 119.6, 110.5, 88.2, 82.9, 81.7, 62.0, 41.3, 26.9; IR (film): $\tilde{\nu}$ = 3434, 3342, 3019, 1718, 1614, 1335, 1216, 1150 cm^{-1}; $[\alpha]_D^{25}$ = −180 (c = 0.65 in $CHCl_3$).

N_b-Trityl-L-tryptophan *tert*-butyl ester (13): *N*,*N*′-Diisopropyl-*O*-*tert*-butylisourea (36.0 g, 179 mmol) was added to a 0 °C solution of crude N_b-trityl-L-tryptophan (40.0 g, 89.7 mmol) and CH_2Cl_2 (200 mL). The resulting mixture was allowed to warm to rt overnight and after 36 h, was filtered through a pad of silica gel (Et_2O), and concentrated. This crude residue was purified by chromatography on silica gel (8:1 hexanes/Et_2O then 3:1 hexanes/Et_2O then 1:1 Et_2O/hexanes then 3:1 Et_2O/hexanes) to give **13** (34.0 g, 76%) as a near colorless foam that was homogeneous by TLC analysis: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.02 (s, 1H), 7.58 (d, J = 7.6 Hz, 1H), 7.46 (d, J = 7.3 Hz, 6H), 7.35–7.04 (m, 12H), 6.91 (s, 1H), 3.67 (brs, 1H), 3.15–3.02 (m, 2H), 2.72 (brs,1H), 1.00 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.2, 146.3, 136.0, 128.7, 127.9, 127.6, 126.1, 123.1, 121.6, 119.3, 119.0, 111.6, 110.9, 80.1, 71.1, 57.2, 31.8, 27.7; IR (film): $\tilde{\nu}$ = 3423, 3057, 2977, 2930, 1717, 1940, 1455, 1217, 1152, 747 cm^{-1}; ES-MS: *m*/*z*: calcd for $C_{34}H_{35}N_2O_2$ $[M+H]^+$: 503.26, found: 503.26; $[\alpha]_D^{25}$ = 2.98 (c = 1.0 in $CHCl_3$).

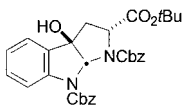


3a-Hydroxypyrroloindoline *tert*-butyl ester (14): A solution of DMDO (≈0.08M in acetone, 250 mL, 19.9 mmol) was added in one portion to a −78 °C solution of **13** (10.0 g, 19.9 mmol) and CH_2Cl_2 (100 mL). The resulting solution was aged at −78 °C for 30 min and then concentrated to give the crude hydroxypyrroloindoline as a yellow oil.



A solution of this crude residue, HOAc (50 mL), MeOH (100 mL), and CH_2Cl_2 (200 mL) was maintained at rt for 2 h and then concentrated. The resulting residue was purified by chromatography on silica gel (8:1 hexanes/Et_2O then 3:1 hexanes/Et_2O then 3:1 Et_2O/hexanes then Et_2O then EtOAc then MeOH) to give **14** (3.00 g, 55%) as a tan solid that was homogeneous by TLC analysis: m.p. 197–198 °C; ^{1}H NMR (500 MHz, MeOH): δ = 7.21 (d, J = 7.1 Hz, 1H), 7.07 (dt, J = 7.9, 1.1 Hz, 1H), 6.72 (t, J = 7.2 Hz, 1H), 6.57 (d, J = 7.9 Hz, 1H), 4.94 (s, 1H), 3.56 (dd, J = 9.4, 6.4 Hz, 1H), 2.67 (dd, J = 12.4, 9.5 Hz, 1H), 2.43 (dd, J = 12.4, 6.4 Hz, 1H), 1.45 (s, 9H); ^{13}C NMR (125 MHz, MeOH): δ = 173.7, 151.8, 132.5, 130.7, 125.0, 119.8, 110.8, 90.1, 86.1, 82.7, 61.1, 46.3, 28.3; IR (film): $\tilde{\nu}$ = 3442, 3395, 3215, 2994, 2911, 1736, 1610, 1436, 1310, 1051, 953, 698 cm^{-1}; ES-MS: *m*/*z*: calcd for $C_{15}H_{21}N_2O_3$ $[M+H]^+$: 277.15, found: 277.1; $[\alpha]_D^{25}$ = −89.6 (c = 1.0 in MeOH).

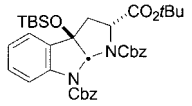
Pyrroloindoline *tert*-butyl ester 15: Freshly prepared Al(Hg) (10 g) was added to a vigorously stirred mixture of crude **11**



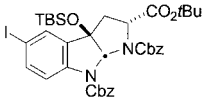
(6.00 g, 11.6 mmol) and THF/H_2O (10:1, 200 mL) at 0 °C. The resulting mixture turned from bright yellow to gray over 2 h indicating consumption of **11**. The mixture was filtered through a pad of celite (EtOAc) and concentrated. The crude residue was used without further purification.

Neat pyridine (5.60 mL, 69.8 mmol) was added to a 0 °C solution of the crude residue, $ClCO_2Bn$ (5.25 mL, 34.9 mmol) and CH_2Cl_2 (40 mL). The resulting solution was allowed to warm to rt overnight and then concentrated. The crude residue was dissolved in EtOAc (100 mL) and washed with 1M HCl (2 × 50 mL), brine (1 × 50 mL), dried ($MgSO_4$), and concentrated. This residue was purified by chromatography on silica gel (8:1 hexanes/Et_2O then 3:1 hexanes/Et_2O then 1:1 Et_2O/hexanes then 3:1 Et_2O/hexanes then Et_2O then EtOAc) to give **15** (3.82 g, 60%) as a near colorless oil that was homogeneous by TLC analysis: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.67 (brs, 1H), 7.45–7.08 (m, 12H), 7.03 (t, J = 7.4 Hz, 1H), 6.09 (s, 1H), 5.31–4.65 (m, 4H), 4.55 (brs, 1H), 4.10 (brs, 1H), 2.75–2.60 (m, 2H), 1.01 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.2, 153.5, 142.5, 136.0, 135.7, 132.3, 130.4, 128.5, 128.3, 127.9, 127.8, 124.0, 123.7, 117.1, 82.2, 82.0, 81.3, 67.6, 67.1, 60.0, 40.2, 27.2; IR (film): $\tilde{\nu}$ = 3410, 2978, 1716, 1453, 1289, 1207, 1018, 735 cm^{-1}; ES-MS: m/z: calcd for $C_{31}H_{32}N_2O_7Na$ $[M+Na]^+$: 567.21, found: 567.3; $[\alpha]_D^{25}$ = −40.5 (c = 1.0 in $CHCl_3$).

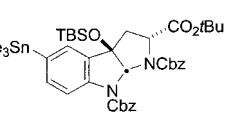
Silylpyrroloindoline *tert*-butyl ester 16: A solution of DBU (8.60 mL, 57.4 mmol) and DMF (50 mL) was added to a solution of **15** (7.80 g, 14.3 mmol), TBSCl (4.40 g, 28.7 mmol), and DMF (50 mL). The resulting solution was warmed to 50 °C for 5 h, cooled, and was then diluted with EtOAc (400 mL) and poured into aqueous 1M HCl (200 mL). The layers were separated and the organic layer was washed with aqueous 1M HCl (3 × 100 mL), saturated aqueous $NaHCO_3$ (1 × 100 mL), brine (2 × 100 mL), dried ($MgSO_4$), and concentrated. The crude residue was purified by chromatography on silica gel (3:1 hexanes/Et_2O then 1:1 Et_2O/hexanes then 3:1 Et_2O/hexanes) to give **16** (7.20 g, 77%) as a colorless oil that was homogeneous by TLC analysis: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.78 (brs, 1H), 7.50–7.10 (m, 12H), 7.05 (t, J = 7.3 Hz, 1H), 6.09 (brs, 1H), 5.42–4.92 (m, 4H), 5.08 (brs, 1H), 4.59 (brs, 1H), 2.83 (d, J = 12.8 Hz, 1H), 2.78–2.72 (m, 1H), 1.03 (s, 9Hs), 0.78 (s, 9H), −0.32 (s, 3H), −0.37 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.2, 153.3, 143.2, 136.2, 136.0, 131.8, 130.6, 128.3, 128.2, 128.1, 128.0, 127.9, 124.3, 123.6, 117.3, 86.8, 81.9, 81.2, 67.4, 67.1, 59.8, 41.1, 27.3, 25.3, 17.7, −3.8, −4.4; IR (film): $\tilde{\nu}$ = 2953, 1718, 1480, 1255, 1142, 1107, 1019 cm^{-1}; ES-MS: m/z: calcd for $C_{37}H_{46}N_2O_7SiNa$ $[M+Na]^+$: 681.30, found: 681.5, 135; $[\alpha]_D^{25}$ = −38.1 (c = 1.0 in $CHCl_3$).



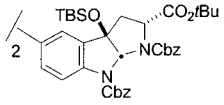
5-Iodo-pyrroloindoline *tert*-butyl ester 17: Neat ICl (1.80 mL, 35.3 mmol) was added to a 0 °C solution of **16** (2.30 g, 3.50 mmol), 2,6-di-*tert*-butyl-4-methyl pyridine (6.70 g, 35.3 mmol), and CH_2Cl_2 (40 mL). The resulting solution was allowed to warm to rt overnight, and after 24 h, was diluted with EtOAc (200 mL), and poured into saturated aqueous $Na_2S_2O_3$ (100 mL). The layers were separated and the organic layer was washed with aqueous 1M HCl (3 × 50 mL), saturated aqueous $NaHCO_3$ (2 × 50 mL), brine (2 × 50 mL), dried ($MgSO_4$), and concentrated. The crude residue was purified by chromatography on silica gel (8:1 hexanes/Et_2O then 3:1 hexanes/Et_2O then 1:1 Et_2O/hexanes) to give **17** (2.24 g, 81%) as a pale yellow glass that was homogeneous by TLC analysis: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.62 (d, J = 1.4 Hz, 1H), 7.60 (s, 1H), 7.39–7.25 (m, 11H), 6.02 (brs, 1H), 5.45–4.97 (m, 4H), 4.56 (brs, 1H), 2.80–2.68 (m, 2H), 1.27 (s, 9H), 0.76 (s, 9H), −0.31 (s, 3H), −0.37 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.9, 153.1, 143.0, 139.3, 136.1, 135.7, 134.7, 133.2, 128.4, 128.2, 128.0, 119.5, 86.2, 81.9, 81.7, 67.8, 67.4, 59.6, 40.7, 27.5, 25.3, 17.7, −3.5, −4.3; IR (film): $\tilde{\nu}$ = 2953, 2856, 1720, 1473, 1255, 1146, 837 cm^{-1}; ES-MS: m/z: calcd for $C_{37}H_{45}N_2O_7SiINa$ $[M+Na]^+$: 807.19, found: 807.4, 135; $[\alpha]_D^{25}$ = −59.0 (c = 1.0 in $CHCl_3$).



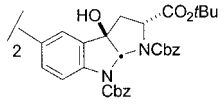
5-Trimethylstannyl-pyrroloindoline *tert*-butyl ester 18: Neat Me_6Sn_2 (2.76 g, 8.41 mmol) was added to a solution of **17** (3.30 g, 4.21 mmol), $[Pd(Ph_3P)_4]$ (0.49 g, 0.421 mmol), and THF (15.0 mL) at rt. The resulting solution was warmed to 60 °C for 5 h, allowed to cool to rt, and then diluted with EtOAc (100 mL), and poured into saturated aqueous $NaHCO_3$ (100 mL). The layers were separated and the organic layer was washed with saturated aqueous $NaHCO_3$ (2 × 50 mL), brine (3 × 50 mL), dried (Na_2SO_4), and concentrated. The crude residue was purified by chromatography on silica gel (8:1 hexanes/Et_2O then 3:1 hexanes/Et_2O then 1:1 Et_2O/hexanes then 3:1 Et_2O/hexanes) to give **18** (3.10 g, 89%) as a pale yellow glass that was homogeneous by TLC analysis: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.70 (brs, 1H), 7.60–7.35 (m, 12H), 6.02 (brs, 1H), 5.50–4.85 (m, 4H), 4.56 (brs, 1H), 2.84 (d, J = 12.9 Hz, 1H), 2.80–2.70 (m, 1H), 1.10 (s, 9H), 0.74 (s, 9H), 0.26 (s, 9H), −0.37 (s, 3H), −0.44 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.4, 153.4, 143.6, 137.9, 136.3, 136.1, 131.7, 131.5, 128.3, 128.0, 117.0, 86.5, 82.0, 81.1, 67.5, 67.2, 59.8, 40.9, 27.3, 25.4, 17.8, −3.7, −4.4, −9.6; IR (film): $\tilde{\nu}$ = 2953, 1718, 1479, 1338, 1302, 1149, 1103, 1020 cm^{-1}; ES-MS: m/z: calcd for $C_{40}H_{54}N_2O_7SiSnNa$ $[M+Na]^+$: 843.26, found: 843.4, 135; $[\alpha]_D^{25}$ = −46.9 (c = 1.0 in $CHCl_3$).



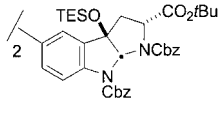
3a-*tert*-Butyldimethylsiloxy-pyrroloindoline *tert*-butyl ester dimer 19: A solution of stannane **18** (900 mg, 1.10 mmol) in DMF (8 mL) was added to a solution of iodide **17** (781 mg, 1.00 mmol), $[Pd_2dba_3]$ (96.0 mg, 0.100 mmol), Ph_3As (61.0 mg, 0.199 mmol), and DMF (9.0 mL) at rt. The resulting mixture was warmed to 45 °C for 22 h, allowed to cool to rt and then diluted with EtOAc (100 mL) and poured into saturated aqueous $NaHCO_3$ (100 mL). The layers were separated and the organic layer was washed with saturated aqueous $NaHCO_3$ (2 × 50 mL), brine (3 × 50 mL), dried (Na_2SO_4), and concentrated. The crude residue was purified by chromatography on silica gel (8:1 hexanes/Et_2O then 3:1 hexanes/Et_2O then 1:1 Et_2O/hexanes then 3:1 Et_2O/hexanes) to give **19** (722 mg, 55%) as a light yellow oil that was homogeneous by TLC analysis: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.80 (brs, 2H), 7.43 (d, J = 8.1 Hz, 2H), 7.40–7.25 (m, 22H), 6.10 (brs, 2H), 5.50–4.80 (m, 8H), 4.59 (brs, 2H), 2.84 (d, J = 12.9 Hz, 2H), 2.80–2.65 (m, 2H), 0.97 (brs, 18H), 0.77 (s, 18H), −0.35– −0.40 (m, 12H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.2, 153.3, 142.6, 136.6, 136.2, 136.0, 132.6, 129.4, 128.4, 128.2, 128.1, 128.0, 122.9, 117.6, 86.0, 82.3, 81.3, 67.6, 67.3, 59.8, 41.1, 27.3, 25.4, 17.8, −3.6, −4.2; IR (film): $\tilde{\nu}$ = 2953, 1718, 1477, 1303, 1147, 1103, 837 cm^{-1}; ES-MS: m/z: calcd for $C_{74}H_{90}N_4O_{14}Si_2Na$ $[M+Na]^+$: 1337.59, found: 1337.8, 135; $[\alpha]_D^{25}$ = −78.0 (c = 1.0 in $CHCl_3$).



3a-Hydroxypyrroloindoline *tert*-butyl ester dimer 20: A solution of TBAF (1M in THF, 2.28 mL) was added to a 0 °C solution of **19** (2.00 g, 1.52 mmol) and THF (10.0 mL). The resulting solution was maintained at 0 °C for 2 h and was then diluted with EtOAc (100 mL) and poured into saturated aqueous $NaHCO_3$ (100 mL). The layers were separated and the organic layer was washed with 1M HCl (2 × 50 mL), saturated aqueous $NaHCO_3$ (2 × 50 mL), brine (3 × 50 mL), dried ($MgSO_4$), and concentrated. The crude residue was purified by chromatography on silica gel (8:1 hexanes/Et_2O then 3:1 hexanes/Et_2O then 1:1 Et_2O/hexanes then 3:1 Et_2O/hexanes then Et_2O then EtOAc) to give **20** (1.40 g, 85%) as a colorless oil that was homogeneous by TLC analysis: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.71 (brs, 2H), 7.41 (s, 2H), 7.35–7.18 (m, 22H), 6.08 (s, 2H), 5.22–4.73 (m, 8H), 4.54 (d, J = 7.8 Hz, 2H), 3.93 (brs, 2H), 2.80–2.60 (m, 4H), 0.93 (s, 18H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.5, 153.5, 142.0, 136.0, 135.8, 133.0, 129.1, 128.4, 128.1, 128.0, 122.1, 117.3, 85.0, 82.5, 81.6, 67.8, 67.3, 60.2, 40.8, 27.2; IR (film): $\tilde{\nu}$ = 3424, 3018, 1712, 1478, 1410, 1215, 1110, 755 cm^{-1}; ES-MS: m/z: calcd for $C_{62}H_{62}N_4O_{14}Na$ $[M+Na]^+$: 1109.42, found: 1109.7, 135; $[\alpha]_D^{25}$ = −122 (c = 0.6 in $CHCl_3$).



Pyrroloindoline *tert*-butyl ester dimer 21: A solution of DBU (0.45 mL, 3.04 mmol) and DMF (5.0 mL) was added to a solution of **20** (1.10 g, 1.01 mmol), TESCl (1.02 mL, 6.08 mmol), and DMF (8.0 mL) at rt. The resulting solution was warmed to 50 °C for 5 h, cooled, and was then diluted with EtOAc (200 mL) and poured into aqueous 1M HCl (100 mL). The layers were separated and the organic layer was washed with 1M HCl (2 × 50 mL), saturated aqueous $NaHCO_3$ (1 × 50 mL), brine (1 × 50 mL), dried ($MgSO_4$), and concentrated. The crude residue was purified by chromatography on silica gel (8:1 hexanes/Et_2O then 3:1 hexanes/Et_2O then 1:1 Et_2O/hexanes then 3:1 Et_2O/hexanes) to



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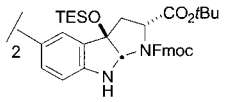
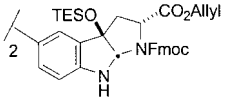
give **21** (1.05 g, 79%) as a near colorless oil that was homogeneous by TLC analysis: ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.81$ (br s, 2H), 7.44 (d, $J =$ 8.5 Hz, 2H), 7.38 (s, 2H), 7.36–7.25 (m, 20H), 6.10 (br s, 2H), 5.52–4.90 (m, 8H), 4.58 (br s, 2H), 2.84 (d, $J = 12.8$ Hz, 2H), 2.80–2.63 (m, 2H), 0.97 (br s, 18H), 0.73 (t, $J = 8.0$ Hz, 18H), 0.38–0.20 (m, 12H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 169.2$, 153.3, 142.5, 136.4, 136.2, 132.7, 129.3, 128.3, 128.0, 122.5, 117.6, 86.2, 82.4, 81.3, 67.6, 67.2, 59.9, 40.8, 27.2, 6.5, 5.4; IR (film): $\tilde{\nu} = 2955$, 1718, 1478, 1340, 1253, 1147, 1102, 1017, 735 cm^{-1}; ES-MS: m/z: calcd for $C_{74}H_{90}N_4O_{14}Si_2Na$ $[M+Na]^+$: 1337.59, found: 1337.9, 135; $[\alpha]_D^{25} = -74.1$ ($c = 1.0$ in $CHCl_3$).

Pyrroloindoline dimer 22: A solution of **21** (920 mg, 0.700 mmol) and EtOAc (20.0 mL) was charged with 10% Pd/C (100 mg) at rt. The resulting mixture was evacuated/purged with H_2 (3×) and was then stirred vigorously under 1 atm H_2 for 26 h. The mixture was filtered through a pad of celite (EtOAc) and concentrated.

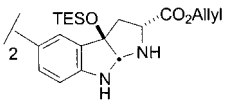


Neat pyridine (0.340 mL, 4.20 mmol) was added to a 0°C solution of the crude residue, Fmoc-HOSu (944 mg, 2.80 mmol) and CH_2Cl_2 (6.0 mL). The resulting solution was allowed to warm to rt overnight and then concentrated. The crude residue was purified by chromatography on silica gel (8:1 hexanes/Et_2O then 3:1 hexanes/Et_2O then 1:1 Et_2O/hexanes then 3:1 Et_2O/hexanes then Et_2O) to give **22** (746 mg, 87%) as a colorless solid that was homogeneous by TLC analysis: m.p. 210–212°C; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.85$–7.09 (m, 20H), 6.64 (dd, $J = 11.2$, 8.1 Hz, 1H), 6.36 (dd, $J = 13.6$, 8.1 Hz, 1H), 5.36–5.26 (m, 2H), 4.75–3.95 (m, 10H), 2.90–2.82 (m, 1.6H), 2.78–2.62 (m, 2.4H), 1.04 (s, 4.5H), 1.02 (s, 4.5H), 1.00 (s, 4.5H), 0.99 (s, 4.5H), 0.94–0.80 (m, 18H), 0.54–0.38 (m, 12H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 169.5$, 169.4, 169.1, 169.0, 154.9, 153.8, 149.5, 149.4, 148.8, 148.7, 144.1, 143.9, 143.5, 141.7, 141.3, 141.2, 141.1, 132.8, 132.5, 129.2, 128.9, 128.8, 127.8, 127.7, 127.5, 127.3, 127.2, 127.1, 127.0, 125.1, 125.0, 124.6, 124.4, 122.9, 122.8, 120.2, 120.0, 119.9, 110.2, 109.6, 109.5, 88.1, 87.3, 82.3, 81.5, 81.4, 81.1, 67.7, 66.6, 59.6, 59.3, 47.3, 47.2, 42.7, 42.1, 27.4, 27.3, 6.8, 6.7, 5.5, 5.3; IR (film): $\tilde{\nu} = 3427$, 3019, 1742, 1708, 1420, 1215, 1119, 747 cm^{-1}; ES-MS: m/z: calcd for $C_{72}H_{86}N_4O_{10}Si_2Na$ $[M+Na]^+$: 1245.58, found: 1245.9, 135; $[\alpha]_D^{25} = -270$ ($c = 1.0$ in $CHCl_3$).

3a-Triethylsiloxypyrroloindoline allyl ester dimer 23: Neat TESOTf (2.60 mL, 11.4 mmol) was added to a 0°C solution of **22** (696 mg, 0.57 mmol), 2,6-lutidine (3.30 mL, 28.5 mmol), and CH_2Cl_2 (5.0 mL). The resulting solution was allowed to warm to rt overnight, recooled to 0°C, quenched with saturated aqueous $NaHCO_3$ (50 mL), and diluted with EtOAc (100 mL). The layers were separated and the organic layer was washed with aqueous 1M HCl (2× 50 mL), brine (1× 50 mL), dried (Na_2SO_4), and concentrated to give crude diacid. This residue residue was azeotroped with toluene (2× 100 mL) to remove TESOH and was used without further purification.

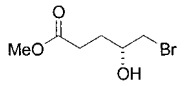


EDCI (656 mg, 3.40 mmol) was added to a 0°C solution of the crude residue, allyl alcohol (3.90 mL, 56.9 mmol), DMAP (10 mg), and CH_2Cl_2 (10.0 mL). The resulting solution was allowed to warm to rt overnight and then concentrated. The crude residue was purified by chromatography on silica gel (8:1 hexanes/Et_2O then 3:1 hexanes/Et_2O then 1:1 Et_2O/hexanes then 3:1 Et_2O/hexanes then Et_2O) to give **23** (530 mg, 78%) as a near colorless oil that was homogeneous by TLC analysis: ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.90$–7.15 (m, 20H), 6.63 (t, $J = 8.0$ Hz, 0.8H), 6.39 (t, $J =$ 8.0 Hz, 1.2H), 5.55–5.39 (m, 2H), 5.32–5.21 (m, 2H), 5.10–4.92 (m, 4H), 4.79–3.85 (m, 14H), 2.94–2.65 (m, 4H), 0.95–0.81 (m, 18H), 0.55–0.31 (m, 12H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 170.2$, 169.9, 154.7, 153.9, 149.5, 149.4, 148.7, 148.6, 144.0, 143.8, 143.5, 141.6, 141.2, 141.1, 132.5, 132.3, 131.5, 131.4, 129.0, 128.9, 128.6, 127.8, 127.7, 127.6, 127.5, 127.3, 127.2, 127.0, 126.9, 124.8, 124.7, 124.4, 122.7, 122.6, 120.2, 120.0, 119.9, 118.4, 118.0, 110.2, 110.0, 87.8, 86.9, 82.1, 81.6, 67.5, 66.7, 65.8, 65.6, 58.9, 58.7, 47.1, 42.2, 41.8, 6.7, 5.4, 5.4; IR (film): $\tilde{\nu} = 3419$, 2954, 1750, 1706, 1481, 1305, 1142, 908, 741 cm^{-1}; ES-MS: m/z: calcd for $C_{70}H_{78}N_4O_{10}Si_2Na$ $[M+Na]^+$: 1213.51, found: 1213.8, 135; $[\alpha]_D^{25} = -263$ ($c =$ 0.55 in $CHCl_3$).



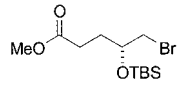
Pyrroloindoline allyl ester dimer 24: Piperidine (163 μL, 1.65 mmol) was added to a 0°C solution of **23** (490 g, 0.412 mmol) and CH_3CN (4.0 mL). The resulting solution was allowed to warm to rt over 5 h and then concentrated. The crude residue was purified by chromatography on silica gel (8:1 hexanes/Et_2O then 3:1 hexanes/Et_2O then 1:1 Et_2O/hexanes then 3:1 Et_2O/hexanes then Et_2O then EtOAc) to give **24** (281 mg, 92%) as a near colorless oil that was homogeneous by TLC analysis: ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.30$ (s, 2H), 7.23 (dd, $J =$ 8.1, 1.4 Hz, 2H), 6.58 (d, $J = 8.1$ Hz, 2H), 5.65–5.50 (m, 2H), 5.08 (d, $J =$ 17.2 Hz, 2H), 5.00 (d, $J = 10.4$, 2H), 4.87 (s, 2H), 4.30–4.22 (m, 4H), 4.01 (dd, 7.0, 5.4 Hz, 2H), 2.68 (dd, $J = 12.7$, 7.4 Hz, 2H), 2.52 (dd, $J = 12.7$, 5.3 Hz, 2H), 0.84 (t, $J = 8.0$ Hz, 18H), 0.49–0.33 (m, 12H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 173.0$, 148.2, 132.7, 131.6, 131.2, 128.1, 122.8, 118.3, 110.5, 90.2, 84.9, 65.5, 59.5, 44.6, 6.7, 5.6; IR (film): $\tilde{\nu} = 3365$, 2953, 1735, 1619, 1482, 1240, 1117, 1008, 740 cm^{-1}; ES-MS: m/z: calcd for $C_{40}H_{59}N_4O_6Si_2$ $[M+H]^+$: 747.40, found: 747.7, 135; $[\alpha]_D^{25} = -77.8$ ($c = 0.65$, $CHCl_3$).

Methyl-5-bromo-4*R*-hydroxypentanoate (26): A solution of NaOMe in MeOH (25% by weight in MeOH, 25.4 mL, 111 mmol) was added to a solution of **25** (15.0 g, 55.6 mmol) and MeOH (200 mL) at rt. After 20 min, the reaction was quenched with glacial HOAc until pH ≈ 7 and concentrated. The crude residue was dissolved in Et_2O (100 mL) and H_2O (100 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (5× 75 mL). The combined organic layers were washed with brine (1× 100 mL), dried ($MgSO_4$), and concentrated.

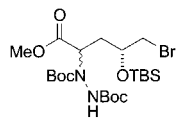


Glacial HOAc (9.50 mL, 167 mmol) was added to a 0°C solution of the crude epoxy ester, LiBr (14.5 g, 167 mmol) and THF (100 mL). The reaction was allowed to warm to rt overnight and then diluted with Et_2O (100 mL) and H_2O (100 mL). The layers were separated and the organic layer was washed with cold saturated aqueous $NaHCO_3$ (2× 50 mL), brine (1× 50 mL), dried (Na_2SO_4), and concentrated. The crude residue was purified by chromatography on silica gel (3:1 hexanes/Et_2O then 3:1 Et_2O/hexanes then Et_2O) to give **26** (10.2 g, 93%) as a colorless oil that was homogeneous by TLC analysis: ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 3.90$–3.85 (m, 1H), 3.69 (s, 3H), 3.51 (dd, $J = 10.3$, 3.9 Hz, 1H), 3.39 (dd, $J = 10.4$, 6.7 Hz, 1H), 2.51 (t, $J = 7.1$ Hz, 2H), 2.08–1.80 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 173.8$, 69.7, 51.5, 38.7, 29.8, 29.6; IR (film): $\tilde{\nu} = 3451$, 2953, 1734, 1438, 1174, 1092 cm^{-1}; ES-MS: m/z: calcd for $C_6H_{11}BrO_3Na$ $[M+Na]^+$: 232.98, found: 232.9; $[\alpha]_D^{25} = +6.32$ ($c = 1.0$ in $CHCl_3$).

Methyl-5-bromo-4*R*-*O*-*tert*-butyldimethylsilylpentanoate (27): TBSOTf (8.50 mL, 37.0 mmol) was added to a −78°C solution of **26** (6.50 g, 30.8 mmol), 2,6-lutidine (7.17 mL, 61.6 mmol), and CH_2Cl_2 (50 mL). The reaction was maintained at −78°C for 1 h, warmed to rt for 1 h, quenched with saturated aqueous $NaHCO_3$ (100 mL) and diluted with EtOAc (100 mL). The layers were separated and the organic layer was washed with 1M HCl (2× 50 mL), saturated aqueous $NaHCO_3$ (1× 50 mL), brine (1× 50 mL), dried ($MgSO_4$), and concentrated. The crude residue was purified by chromatography on silica gel (8:1 hexanes/Et_2O then 3:1 hexanes/Et_2O then 1:1 hexanes/Et_2O then 3:1 Et_2O/hexanes) to give **27** (6.51 g, 65%) as a colorless oil that was homogeneous by TLC analysis: ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 3.92$–3.84 (m, 1H), 3.62 (s, 3H), 3.23 (ddd, $J = 14.8$, 10.3, 4.4 Hz, 2H), 2.33 (t, $J = 7.4$ Hz, 2H), 2.15–1.95 (m, 1H), 1.88–1.75 (m, 1H), 0.84 (s, 9H), 0.046 (s, 3H), 0.018 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 173.5$, 70.4, 51.4, 36.8, 30.2, 29.1, 25.6, 17.9, −4.6, −4.9; IR (film): $\tilde{\nu} = 2954$, 1741, 1437, 1256, 1079, 837, 777 cm^{-1}; ES-MS: m/z: calcd for $C_{12}H_{25}BrO_3SiNa$ $[M+Na]^+$: 347.1, found: 347.2; $[\alpha]_D^{25} = +20.4$ ($c = 1.0$ in $CHCl_3$).



Boc-hydrazine methyl esters 28: A solution of **27** (6.20 g, 19.1 mmol) and THF (15.0 mL) was added to a −78°C solution of NaHMDS (1M in THF, 27.0 mL) and THF (30.0 mL). After 20 min, a solution of DBAD (5.27 g, 22.9 mmol) and THF (20.0 mL) was added. The resulting dark yellow solution was maintained at −78°C for 10 min, quenched with HOAc (5.0 mL), warmed to rt and diluted with EtOAc (100 mL) and saturated aqueous $NaHCO_3$ (100 mL). The layers were separated and the organic layer was washed with 1M HCl (2× 50 mL), saturated aqueous $NaHCO_3$ (2× 50 mL), brine (1× 50 mL), dried ($MgSO_4$), and concentrated. The crude residue was purified by chromatography on silica gel (8:1 hexanes/



Et_2O then 3:1 hexanes/Et_2O then 1:1 hexanes/Et_2O) to give **28** (5.53 g, 79%) as a 1:1 mixture of diastereomers as judged by ^1H NMR analysis. This mixture was used without further purification.

A small amount was purified for analysis by chromatography on silica gel (8:1 hexanes/Et_2O then 3:1 hexanes/Et_2O then 1:1 hexanes/Et_2O) to give the desired (*R*,*R*) diastereomer as a colorless oil that was homogeneous by TLC analysis: ^1H NMR (500 MHz, $CDCl_3$): $\delta = 6.40$ (br s, 1H), 4.94 (br m, 1H), 4.25 (br s, 1H), 3.67 (s, 3H), 3.30–3.23 (m, 2H), 2.06–1.96 (m, 2H), 1.40 (br s, 18H), 0.87 (s, 9H), 0.065 (s, 3H), 0.010 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 172.9$, 155.7, 154.9, 81.7, 80.5, 67.0, 56.6, 52.3, 38.4, 35.2, 28.1, 28.0, 25.7, 17.8, −4.5, −5.3; IR (film): $\tilde{\nu} = 3382$, 3327, 2977, 1744, 1719, 1473, 1368, 1255, 1153, 1076, 839, 778 cm^{-1}; ES-MS: *m*/*z*: calcd for $C_{22}H_{43}BrN_2O_7SiNa$ $[M+Na]^+$: 577.2, found: 577.3; $[\alpha]_D^{25} = +8.40$ ($c = 1.0$ in $CHCl_3$).

***trans*- and *cis*-Piperazic methyl esters (29, 30)**: NaH (60% dispersion in oil, 0.61 g, 15.2 mmol) was added to a 0 °C solution of **28** (6.50 g, 11.7 mmol) and DMF (65 mL). After 20 min, the reaction was poured into a mixture of ice-cold EtOAc/1M HCl (1:1, 300 mL). The layers were separated and the organic layer was washed with 1M HCl (2 × 50 mL), saturated aqueous $NaHCO_3$ (1 × 50 mL), brine (1 × 50 mL), dried ($MgSO_4$), and concentrated. The crude residue was purified by chromatography on silica gel (8:1 hexanes/Et_2O then 3:1 hexanes/Et_2O then 1:1 hexanes/Et_2O) to give **29** (3.0 g, 44%) followed by **30** (2.20 g, 37%), both as colorless oils homogeneous by TLC analysis: *trans*-(**29**): ^1H NMR (500 MHz, $CDCl_3$): $\delta = 5.07–4.83$ (m, 1H), 4.23–3.98 (m, 2H), 3.72 (s, 3H), 3.75–2.50 (m, 1H), 2.35–2.19 (m, 1H), 1.70–1.65 (m, 1H), 1.47 (s, 9H), 1.44 (s, 9H), 0.87 (s, 9H), 0.036 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 170.4$, 154.1, 153.7, 81.9, 80.5, 63.0, 54.3, 52.1, 49.5, 33.8, 28.2, 25.7, 18.0, −4.8; IR (film): $\tilde{\nu} =$ 2976, 1736, 1708, 1393, 1254, 1158, 1096, 878 cm^{-1}; ES-MS: *m*/*z*: calcd for $C_{22}H_{42}N_2O_7SiNa$ $[M+Na]^+$: 497.3, found: 497.3; $[\alpha]_D^{25} = -36.9$ ($c = 1.0$ in $CHCl_3$); *cis*-(**30**): ^1H NMR (500 MHz, $CDCl_3$): $\delta = 5.00–4.75$ (m, 1H), 4.10 (d, $J = 13.3$ Hz, 0.70H), 3.89–3.84 (m, 1.3H), 3.66 (s, 3H), 3.00 (d, $J =$ 13.2 Hz, 0.35H), 2.79 (d, $J = 13.2$ Hz, 0.65H), 1.85–1.79 (m, 1H), 1.46–1.39 (m, 18H), 0.84 (s, 3H), 0.80 (s, 6H), 0.009 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 170.8$, 170.5, 154.7, 154.5, 154.2, 152.3, 81.5, 80.0, 79.8, 63.3, 63.2, 52.0, 51.9, 51.7, 51.6, 50.8, 48.6, 32.7, 28.2, 28.1, 25.6, 25.5, 18.0, −4.9, −5.2, −5.3, −5.4; IR (film): $\tilde{\nu} =$ 2976, 1768, 1735, 1700, 1418, 1365, 1173, 1133, 1095, 882 cm^{-1}; ES-MS: *m*/*z*: calcd for $C_{22}H_{42}N_2O_7SiNa$ $[M+Na]^+$: 497.3, found: 497.2; $[\alpha]_D^{25} = +12.8$ ($c = 1.0$ in $CHCl_3$).

Piperazic acid methyl ester (31 from 30): TFA (20 mL) was added to **30** (2.30 g, 4.85 mmol) and CH_2Cl_2 (20 mL) at 0 °C. The reaction was maintained at 0 °C for 30 min, at rt for 3 h and concentrated.

TeocCl (0.88 mL, 4.85 mmol) was added to a 0 °C solution of this crude residue, pyridine (1.18 mL, 14.6 mmol), and CH_2Cl_2 (20 mL). The reaction was allowed to warm to rt overnight and was then diluted with EtOAc (100 mL) and 1M HCl (50 mL). The layers were separated and the organic layer was washed with 1M HCl (2 × 50 mL), saturated aqueous $NaHCO_3$ (1 × 50 mL), brine (1 × 50 mL), dried ($MgSO_4$), and concentrated. The crude residue was purified by chromatography on silica gel (3:1 hexanes/Et_2O then 1:1 hexanes/Et_2O then 3:1 Et_2O/hexanes then Et_2O then EtOAc) to give **31** (1.73 g, 92%) as a colorless solid homogeneous by TLC analysis.

Hydroxypiperazic acid methyl ester (33): A solution of TBAF (1M in THF, 21.2 mL) was added to a 0 °C solution of **29** (6.70 g, 14.1 mmol) and THF (50 mL). The resulting solution was maintained at 0 °C for 2 h and then poured into saturated aqueous $NaHCO_3$ (200 mL) and diluted with EtOAc (100 mL). The layers were separated and the organic layer was washed with 1M HCl (2 × 50 mL), saturated aqueous $NaHCO_3$ (2 × 50 mL), brine (3 × 50 mL), dried ($MgSO_4$), and concentrated. The crude residue was purified by chromatography on silica gel (3:1 hexanes/Et_2O then 1:1 hexanes/Et_2O then 3:1 Et_2O/hexanes then Et_2O then EtOAc) to give **33** (4.06 g, 80%) as a colorless oil that was homogeneous by TLC analysis: ^1H NMR (500 MHz, $CDCl_3$): $\delta = 5.03$ (br s, 0.80H), 4.83 (br s, 0.20H), 4.25–4.20 (m, 0.6H), 4.10–3.92 (m, 1.4H), 3.64 (s, 3H), 2.90–2.40 (m, 2H), 2.34–2.21 (m, 1H), 1.60–1.50 (m, 1H), 1.46 (s, 9H), 1.43 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 171.4$, 155.3, 155.1, 83.3, 82.0, 63.1, 55.3, 53.3, 50.3, 34.2, 29.3; IR (film): $\tilde{\nu} = 3460$, 2978, 1709, 1395, 1326, 1158, 1087, 993 cm^{-1}; ES-MS: *m*/*z*: calcd for $C_{16}H_{28}N_2O_7Na$ $[M+Na]^+$: 383.18, found: 383.1, 135; $[\alpha]_D^{25} = -48.0$ ($c = 1.0$ in $CHCl_3$).

Piperazic lactone (34 from 33): DBU (5.21 mL, 34.9 mmol) was added to **33** (6.30 g, 17.5 mmol) and toluene (200 mL). The reaction was warmed to reflux using a Dean–Stark trap filled with activated 4 Å molecular sieves. After 52 h, the reaction was cooled to rt, diluted with EtOAc (100 mL), and 1M HCl (100 mL). The layers were separated and the organic layer was washed with 1M HCl (2 × 50 mL), saturated aqueous $NaHCO_3$ (1 × 50 mL), brine (1 × 50 mL), dried ($MgSO_4$), and concentrated. The crude residue was purified by chromatography on silica gel (3:1 hexanes/Et_2O then Et_2O) to give an 8:1 mixture (by ^1H NMR) of **34**:**33** as a colorless solid. Trituration of this solid with hexanes/Et_2O 20:1 gave a 15–20:1 mixture (by ^1H NMR) of **34**:**33** (4.00 g, 69%) as a colorless solid which was used without further purification.

Piperazic ester (31 from 34): Solid **34** (4.70 g, 14.3 mmol) was added to TFA (50 mL) at 0 °C. The resulting solution was maintained at 0 °C for 30 min, at rt for 4 h, and then recooled to 0 °C. MeOH (60.0 mL) was added, the reaction was allowed to come to rt overnight, and then concentrated.

TeocCl (3.13 mL, 17.2 mmol) was added to a −30 °C solution of this crude residue, pyridine (11.6 mL, 143 mmol), and CH_2Cl_2 (150 mL). The resulting solution was allowed to come to rt overnight and then concentrated. The crude residue was purified by chromatography on silica gel (8:1 hexanes/Et_2O then 3:1 hexanes/Et_2O then 1:1 hexanes/Et_2O then 3:1 Et_2O/hexanes then Et_2O then EtOAc) to give the secondary alcohol (3.60 g, 84%) as a colorless oil that was homogeneous by TLC analysis: ^1H NMR (500 MHz, $CDCl_3$): $\delta = 4.20–4.17$ (m, 2H), 4.1–4.07 (br s, 1H), 3.81 (s, 3H), 3.80–3.75 (m, 2H), 3.56 (dd, $J = 10.1$, 3.0 Hz, 1H), 2.98 (br s, 1H), 2.30 (dt, $J = 12.8$, 3.2 Hz, 1H), 1.64–1.62 (m, 1H), 1.02–0.98 (m, 2H), 0.008 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 171.3$, 155.8, 64.6, 64.3, 57.0, 52.3, 50.9, 35.9, 17.8, −1.6; IR (film): $\tilde{\nu} = 3418$, 2954, 1743, 1698, 1250, 1171, 1073, 858 cm^{-1}; ES-MS: *m*/*z*: calcd for $C_{12}H_{24}N_2O_3SiNa$ $[M+Na]^+$: 327.14, found: 327.0; $[\alpha]_D^{25} = +11.3$ ($c = 1.0$ in $CHCl_3$).

TBSOTf (5.87 mL, 25.6 mmol) was added to a −78 °C solution of the above alcohol (4.30 g, 14.1 mmol), 2,6-lutidine (6.63 mL, 56.6 mmol), and CH_2Cl_2 (50 mL). After 4 h, the reaction was quenched with saturated aqueous $NaHCO_3$ (100 mL) and diluted with EtOAc (300 mL). The layers were separated and the organic layer was washed with 1M HCl (2 × 50 mL), saturated aqueous $NaHCO_3$ (1 × 50 mL), brine (1 × 50 mL), dried ($MgSO_4$), and concentrated. The crude residue was purified by chromatography on silica gel (8:1 hexanes/Et_2O then 3:1 hexanes/Et_2O then 1:1 hexanes/Et_2O then 3:1 Et_2O/hexanes then Et_2O) to give **31** (5.80 g, 98%) as a colorless solid that was homogeneous by TLC analysis: m.p. 71–72 °C; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 4.42–4.15$ (m, 4H), 3.70 (s, 3H), 3.69–3.54 (m, 1H), 3.51 (dd, $J = 11.7$, 3.0 Hz, 1H), 2.75 (br s, 1H), 2.22–2.19 (m, 1H), 1.76–1.55 (m, 1H), 1.10–1.00 (m, 2H), 0.84 (s, 9H), 0.044 (s, 3H), 0.038 (s, 3H), 0.004 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 170.7$, 155.9, 65.6, 64.7, 57.4, 52.3, 51.4, 37.6, 25.8, 18.1, 17.9, −1.35, −1.42, −4.64; IR (film): $\tilde{\nu} = 2954$, 1747, 1699, 1252, 1171, 1094, 838 cm^{-1}; ES-MS: *m*/*z*: calcd for $C_{18}H_{38}N_2O_5Si_2Na$ $[M+Na]^+$: 441.22, found: 441.3; $[\alpha]_D^{25} = -20.5$ ($c = 1.0$ in $CHCl_3$).

Penteoic acid (36): 2M LiOH (100 mL) was added to a vigorously stirred mixture of **35** (19.3 g, 38.9 mmol) and THF (100 mL) at 0 °C. After 3 h, the mixture was diluted with Et_2O (100 mL) and the layers were separated. The organic layer was extracted with 1M NaOH (3 × 50 mL) and the organic layer was discarded. The combined aqueous layers were acidified with conc. HCl until a pH 2–3 and extract-

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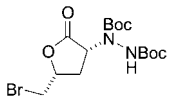
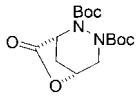
ed with EtOAc (3 × 100 mL). The combined organic layers were dried (Na_2SO_4) and concentrated to give **36** (9.10 g, 71 %) as a colorless oil which was used without further purification.

A small amount of the crude residue was purified for analysis by chromatography on silica gel (8:1 hexanes/Et_2O then 3:1 hexanes/Et_2O then 1:1 hexanes/Et_2O then 3:1 Et_2O/hexanes then Et_2O): ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 9.76$ (br s, 1H), 6.74 (br s, 1H), 5.80–5.61 (m, 1H), 5.21–5.00 (m, 2H), 2.85–2.49 (m, 2H), 1.60–1.37 (m, 18); ^{13}C NMR (125 MHz, $CDCl_3$, 55 °C): $\delta = 171.6$, 154.1, 134.1, 117.8, 84.0, 64.6, 61.8, 33.5, 28.1; IR (film): $\tilde{\nu} = 3582$, 3284, 2980, 1717, 1393, 1369, 1151 cm^{-1}; ES-MS: *m*/*z*: calcd for $C_{15}H_{27}N_2O_6$ $[M+H]^+$: 331.19, found: 331.19; $[\alpha]_D^{25} = +13.7$ ($c = 0.46$, $CHCl_3$).

***cis*-Bromo lactone 37**: Solid NBS (1.94 g, 11.0 mmol) was added to a 0 °C solution of crude acid **36** (3.60 g, 11.0 mmol) and toluene (75.0 mL). After 45 min, the resulting orange solution was diluted EtOAc (100 mL) and quenched with saturated aqueous $Na_2S_2O_3$ (100 mL). The layers were separated and the organic layer was washed with brine (1 × 100 mL), dried ($MgSO_4$), and concentrated. The crude residue was purified by chromatography on silica gel (8:1 hexanes/Et_2O then 3:1 hexanes/Et_2O then 1:1 hexanes/Et_2O then 3:1 Et_2O/hexanes) to give the *trans* diastereomer (650 mg, 15 %) and **37** (2.92 g, 65 %) both as colorless solids that were homogeneous by TLC analysis: ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 6.50$ (br s, 1H), 5.21 (br s, 0.8H), 4.95 (br s, 0.2H), 4.65–4.57 (m, 1H), 3.58–3.45 (m, 2H), 2.76–2.65 (m, 1H), 2.40–2.21 (m, 1H), 1.50 (s, 18H); ^{13}C NMR (125 MHz, $CDCl_3$, 55 °C): $\delta = 171.9$, 155.5, 154.1, 82.8, 81.8, 75.3, 58.7, 32.7, 30.7, 28.2, 28.1; IR (film): $\tilde{\nu} = 3311$, 2978, 1798, 1735, 1709, 1368, 1243, 1163, 1015, 758 cm^{-1}; ES-MS: *m*/*z*: calcd for $C_{15}H_{26}BrN_2O_6$ $[M+H]^+$: 409.10, found: 409.10; $[\alpha]_D^{25} = -23.1$ ($c = 0.52$, $CHCl_3$).

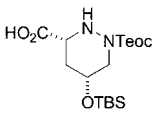


Piperazic lactone (34 from 37): NaHMDS (1 M in THF, 4.70 mL) was added to a 0 °C solution of **37** (1.75 g, 4.27 mmol) and DMF (20.0 mL). After 1.5 h, the reaction was quenched with saturated aqueous NH_4Cl (30 mL) and diluted with EtOAc (100 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 × 25 mL). The combined organic layers were washed with brine (1 × 50 mL), dried ($MgSO_4$) and concentrated.

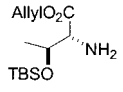


Ac_2O (0.5 mL) was added to the crude residue. After 2 h, the reaction was concentrated and the crude residue was purified by chromatography on silica gel (8:1 hexanes/Et_2O then 3:1 hexanes/Et_2O then 1:1 hexanes/Et_2O then 3:1 Et_2O/hexanes then Et_2O) to give **34** (900 mg, 64 %) as a colorless solid that was homogeneous by TLC analysis: ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 4.87$ (br s, 1H), 4.65 (br s, 1H), 4.11 (br d, 1H), 3.16 (br d, 1H), 2.34–2.29 (m, 1H), 2.02 (d, $J = 12.3$ Hz, 1H), 1.49 (s, 9H), 1.45 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$, 55 °C): $\delta = 170.4$, 154.3, 153.2, 82.7, 82.0, 74.5, 55.8, 47.2, 36.2, 28.2, 28.0; IR (film): $\tilde{\nu} = 2978$, 2852, 1797, 1707, 1477, 1368, 1254, 1151, 1023, 936 cm^{-1}; ES-MS: *m*/*z*: calcd for $C_{15}H_{24}N_2O_6Na$ $[M+Na]^+$: 351.16, found: 351.2; $[\alpha]_D^{25} = +13.8$ ($c = 0.5$ in $CHCl_3$).

***cis*-Piperazic acid (32)**: 2 M LiOH (30 mL) was added to a 0 °C solution of **31** (5.10 g, 12.2 mmol) and THF (50 mL). After 10 min, the reaction was diluted with EtOAc (100 mL) and acidified with 2 M HCl until a pH 2–3 was reached. The layers were separated and the aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine (2 × 50 mL), dried (Na_2SO_4), and concentrated to give **32** (5.0 g, ≈100 %) as a near colorless oil. Analysis of the crude ^{1}H NMR showed the absence of the methyl ester singlet at $\delta = 3.64$. This crude acid was used without further purification.



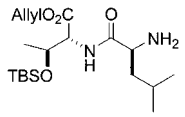
D-Threonine allyl ester 38: A mixture of allyl alcohol (40.0 mL, 0.592 mol), D-threonine (8.00 g, 67.3 mmol), *p*-TsOH (15.3 g, 80.7 mmol), and C_6H_6 (200 mL) was refluxed for 42 h using a Dean–Stark trap and then concentrated. The crude salt was used without further purification.



TBSCl (22.0 g, 0.148 mol) was added to a 0 °C mixture of the crude residue, imidazole (23.0 g, 0.337 mol) and CH_2Cl_2 (150 mL). The mixture was allowed to come to rt overnight and then concentrated. The crude residue was dissolved in EtOAc (300 mL), washed with 1 M NaOH (4 × 50 mL), brine (1 × 50 mL), dried (Na_2SO_4), and concentrated to give **38** (≈21.0 g, >100 %) as a near colorless oil that was used without further purification.

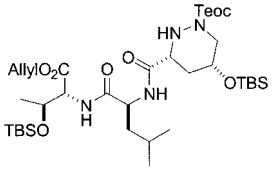
A small amount was purified for analysis by chromatography on silica gel (3:1 hexanes/Et_2O then 3:1 Et_2O/hexanes then Et_2O then EtOAc) to give **38** as a colorless oil that was homogeneous by TLC analysis: ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 5.84–5.78$ (m, 1H), 5.23 (d, $J = 17.1$ Hz, 1H), 5.13 (d, 10.4 Hz, 1H), 4.52 (dd, $J = 13.1$, 5.9 Hz, 1H), 4.43 (dd, $J = 13.1$, 5.9 Hz, 1H), 4.21–4.18 (m, 1H), 3.18–3.16 (m, 1H), 1.48 (s, 2H), 1.13 (d, $J = 6.3$ Hz, 3H), 0.73 (s, 9H), 0.072 (s, 3H), −0.13 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 173.9$, 131.7, 118.4, 69.3, 65.4, 60.5, 25.4, 20.6, 17.6, −4.6, −5.5; IR (film): $\tilde{\nu} = 3390$, 2955, 2890, 1742, 1253, 1156, 1076, 837 cm^{-1}; ES-MS: *m*/*z*: calcd for $C_{13}H_{28}NO_3Si$ $[M+H]^+$: 274.18, found: 274.2, 135; $[\alpha]_D^{25} = +16.8$ ($c = 1.0$ in $CHCl_3$).

Dipeptide 40: EDCI (9.80 g, 51.3 mmol) was added to a 0 °C solution of Fmoc-L-leucine (**39**) (18.0 g, 51.3 mmol), DMAP (20 mg), and CH_2Cl_2 (150 mL). After 10 min, a solution of crude **38** (≈14.0 g, 51.3 mmol) and CH_2Cl_2 (100 mL) was added. The reaction mixture was maintained at 0 °C for 2 h and then concentrated. The crude residue was purified by chromatography on silica gel (8:1 hexanes/Et_2O then 3:1 hexanes/Et_2O then 1:1 hexanes/Et_2O) to give the Fmoc-dipeptide (26.0 g, 96 %) as a colorless oil that was homogeneous by TLC analysis: ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.74$ (d, $J = 7.5$ Hz, 2H), 7.74–7.58 (m, 2H), 7.40–7.37 (m, 2H), 7.31–7.26 (m, 2H), 6.77 (d, $J = 9.0$ Hz, 1H), 5.89–5.84 (m, 1H), 5.44 (d, $J = 7.9$ Hz, 1H), 5.31 (dd, $J = 17.2$, 1.1 Hz, 1H), 5.20 (d, $J = 10.4$ Hz, 1H), 4.62–4.22 (m, 8H), 1.78–1.60 (m, 3H), 1.18 (d, $J = 5.9$ Hz, 3H), 0.98 (s, 6H), 0.84 (s, 9H), 0.045 (s, 3H), 0.16 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 172.3$, 169.9, 156.0, 143.6, 141.2, 131.3, 127.6, 126.9, 125.0, 119.8, 118.9, 68.7, 66.9, 66.0, 57.6, 53.5, 47.0, 41.4, 25.5, 24.7, 22.8, 21.9, 20.9, 17.6, −4.5, −5.4; IR (film): $\tilde{\nu} = 3429$, 3301, 2930, 1719, 1672, 1518, 1253, 1095, 1036, 837 cm^{-1}; ES-MS: *m*/*z*: calcd for $C_{34}H_{48}N_2O_6SiNa$ $[M+Na]^+$: 631.3, found: 631.5, 135; $[\alpha]_D^{25} = -27.9$ ($c = 1.0$ in $CHCl_3$).



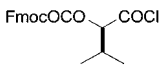
Piperidine (7.50 mL, 76.0 mmol) was added to a 0 °C solution of the Fmoc-dipeptide (25.0 g, 41.1 mmol) and CH_3CN (100 mL). The resulting mixture was allowed to warm to rt over 3 h and then concentrated. The crude residue was purified by chromatography on silica gel (8:1 hexanes/Et_2O then 3:1 hexanes/Et_2O then 1:1 hexanes/Et_2O then 3:1 Et_2O/hexanes then Et_2O then EtOAc) to give **40** (14.5 g, 92 %) as a colorless oil that was homogeneous by TLC analysis: ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.76$ (d, $J = 9.4$ Hz, 1H), 5.82–5.75 (m, 1H), 5.21 (d, $J = 28.1$ Hz, 1H), 5.12 (d, $J = 10.4$ Hz, 1H), 4.51–4.37 (m, 4H), 3.35 (dd, $J = 9.5$, 4.16 Hz, 1H), 1.66–1.58 (m, 2H), 1.34–1.31 (m, 3H), 1.05 (d, $J = 6.2$ Hz, 3H), 0.84 (d, $J = 22$ Hz, 3H), 0.80 (d, $J = 6.1$ Hz, 3H), 0.75 (s, 9H), 0.073 (s, 3H), −0.14 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 175.9$, 170.1, 131.4, 118.5, 68.5, 65.6, 57.3, 53.3, 43.8, 25.4, 24.5, 23.1, 21.2, 20.8, 17.5, −4.6, −5.5; IR (film): $\tilde{\nu} = 3376$, 2955, 2858, 1748, 1673, 1506, 1255, 1156, 1096, 838, 778 cm^{-1}; ES-MS: *m*/*z*: calcd for $C_{19}H_{39}N_2O_4Si$ $[M+H]^+$: 387.3, found: 387.4, 135; $[\alpha]_D^{25} = -12.5$ ($c = 1.0$ in $CHCl_3$).

Tripeptide 41: HATU (6.10 g, 16.1 mmol) was added to a 0 °C solution of amine **40** (9.60 g, 24.5 mmol), crude acid **32** (5.00 g, 12.4 mmol), HOAt (3.40 g, 24.8 mmol), collidine (4.90 mL, 37.1 mmol), and CH_2Cl_2 (100 mL). The reaction mixture was allowed to warm to rt overnight and then concentrated. The crude residue was taken up in EtOAc (100 mL) and washed with 1 M HCl (3 × 50 mL), saturated aqueous $NaHCO_3$ (3 × 50 mL), brine (1 × 50 mL), dried ($MgSO_4$), and concentrated. The crude residue was purified by chromatography on silica gel (3:1 hexanes/Et_2O then 1:1 hexanes/Et_2O then 3:1 Et_2O/hexanes then Et_2O) to give **41** (6.82 g, 72 %) as a colorless oil that was homogeneous by TLC analysis: ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.00–6.98$ (m, 1H), 6.73–6.71 (d, $J = 9.3$ Hz, 1H), 5.92–5.86 (m, 1H), 5.33–5.23 (m, 2H), 4.59–4.46 (m, 5H), 4.22–4.19 (m, 2H), 4.19–4.18 (m, 1H), 3.75–3.72 (m, 1H), 3.42–3.40 (m, 1H), 2.75–2.68



(m, 1H), 2.32–2.30 (m, 1H), 1.71–1.56 (m, 4H), 1.16 (d, $J=6.3$ Hz, 3H), 1.02–0.98 (m, 2H), 0.95 (d, $J=6.3$ Hz, 3H), 0.92 (d, $J=6.2$ Hz, 3H), 0.86 (s, 9H), 0.85 (s, 9H), 0.074 (s, 3H), 0.062 (s, 3H), 0.040 (s, 12H), 0.005 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=172.2$, 170.4, 170.1, 155.7, 131.5, 119.1, 68.5, 66.0, 65.8, 64.5, 58.8, 57.9, 51.4, 50.9, 40.2, 37.4, 25.6, 24.8, 22.8, 22.1, 21.0, 18.0, 17.8, 17.7, −1.5, −4.3, −4.7, −4.8, −5.3; IR (film): $\tilde{\nu}=3358$, 3285, 2955, 2857, 1737, 1698, 1668, 1522, 1252, 1176, 1127, 837 cm^{-1}; ES-MS: m/z: calcd for $C_{36}H_{72}N_4O_8Si_3Na$ $[M+Na]^+$: 795.46, found: 795.5, 135; $[\alpha]_D^{25}=-25.4$ ($c=1.0$ in $CHCl_3$).

Fmoc-L-hydroxyisovaleric acid chloride (42): Neat allyl bromide (22.0 mL, 254 mmol) was added to a 0 °C solution of (*S*)-hydroxy isovaleric acid (10.0 g, 84.8 mmol), Cs_2CO_3 (30.3 g, 93.2 mmol), and DMF (200 mL). After 2 h at 0 °C, the reaction was diluted with EtOAc (100 mL) and 1M HCl (100 mL). The layers were separated and the organic layer was washed with 1M HCl (2 × 50 mL), saturated aqueous $NaHCO_3$ (2 × 50 mL), brine (1 × 50 mL), dried ($MgSO_4$), and concentrated to give a near colorless oil (≈13 g) that was used without further purification.

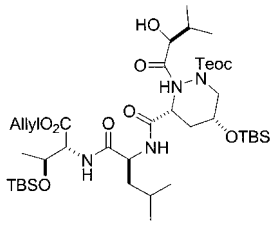


Neat pyridine (7.30 mL, 89.9 mmol) was added to a 0 °C solution of this crude residue, Fmoc-Cl (12.2 g, 47.2 mmol) and CH_2Cl_2 (100 mL). The resulting solution was maintained at 0 °C for 1 h and then concentrated. The crude residue was dissolved in Et_2O (100 mL) and washed with 1M HCl (2 × 50 mL), brine (1 × 50 mL), dried ($MgSO_4$), and concentrated to give a near colorless oil (≈18 g) that was used without further purification.

$PhSiH_3$ (6.60 mL, 53.9 mmol) was added to a 0 °C solution of this crude residue, $[Pd(Ph_3P)_4]$ (1.04 g,0.898 mmol), and THF (150 mL). The resulting solution was allowed to warm to rt overnight and then concentrated. The crude residue was purified by chromatography on silica gel (8:1 hexanes/Et_2O then 3:1 hexanes/Et_2O then 1:1 hexanes/Et_2O then 3:1 Et_2O/hexanes then Et_2O) to give the acid (12.1 g, 78%) as an off-white solid that was homogeneous by TLC analysis: m.p. 152–154 °C; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=7.77$ (d, $J=7.5$ Hz, 2H), 7.63 (dd, $J=10.9$, 7.6 Hz, 2H), 7.42 (t, $J=7.5$ Hz, 2H), 7.31 (t, $J=7.4$ Hz, 2H), 4.90 (d, $J=4.1$ Hz, 1H), 4.52 (dd, $J=9.9$, 6.8 Hz, 1H), 4.40–4.29 (m, 2H), 2.49–2.35 (m, 1H), 1.12 (d, $J=7.0$ Hz, 3H), 0.97 (d, $J=7.0$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=175.6$, 154.9, 143.4, 143.0, 141.2, 127.9, 127.2, 125.3, 125.1, 120.0, 79.3, 70.4, 46.6, 30.1, 18.7, 17.0; IR (film): $\tilde{\nu}=3065$, 3020, 1749, 1719, 1450, 1280, 1217, 996, 757 cm^{-1}; ES-MS: m/z: calcd for $C_{20}H_{20}O_5Na$ $[M+Na]^+$: 363.13, found: 363.1; $[\alpha]_D^{25}=-3.18$ ($c=1.0$ in $CHCl_3$).

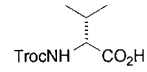
N,N-Dimethyl-2-chloro-propenyl amine (2.20 mL, 16.3 mmol) was added to a 0 °C solution of this acid (3.70 g, 10.9 mmol) and CH_2Cl_2 (30.0 mL). After 45 min, an aliquot was removed and concentrated. ^{1}H NMR inspection of this sample indicated that full conversion to the acid chloride had occurred. The solution of acid chloride was used without further manipulation.

Tetrapeptide 43: A solution of **41** (2.60 g, 3.37 mmol), collidine (4.40 mL, 33.5 mmol), and CH_2Cl_2 (10.0 mL) was added at 0 °C to a freshly prepared solution of **42** (3.70 g, 10.9 mmol) in CH_2Cl_2 (30.0 mL). The reaction mixture was allowed to come to rt overnight and was then quenched with saturated aqueous $NaHCO_3$ (30 mL) and diluted with EtOAc (300 mL). The layers were separated and the organic layer was washed with 1M HCl (3 × 50 mL), saturated aqueous $NaHCO_3$ (2 × 50 mL), brine (1 × 50 mL), dried ($MgSO_4$), and concentrated.

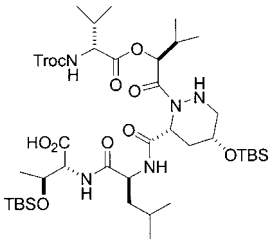


Piperidine (3.30 mL, 33.5 mmol) was added to a 0 °C solution of this crude residue and CH_3CN (50.0 mL). The resulting mixture was maintained at 0 °C for 30 min, at rt for 1 h and then concentrated. The crude residue was purified by chromatography on silica gel (8:1 hexanes/Et_2O then 3:1 hexanes/Et_2O then 1:1 hexanes/Et_2O then 3:1 Et_2O/hexanes then Et_2O) to give **43** (2.70 g, 92%) as a colorless oil that was homogeneous by TLC analysis: ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=8.32$ (d, $J=6.7$ Hz, 1H), 6.71 (d, $J=8.7$ Hz, 1H), 5.91–5.85 (m, 1H), 5.30 (d, $J=7.2$ Hz, 1H), 5.22 (d, $J=10.3$ Hz, 1H), 4.75–3.86 (m, 10H), 3.45–3.36 (m, 1H), 3.25–3.15 (m, 1H), 2.15–1.84 (m, 3H), 1.65 (br s, 3H), 1.11 (d, $J=6.3$ Hz, 3H), 1.06–0.89 (m, 14H), 0.83 (s, 9H), 0.14–−0.03 (m, 21H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=175.9$, 171.9, 170.0, 169.5, 158.0, 131.6, 118.8, 72.9, 69.0, 67.0, 66.1, 65.8, 64.2, 57.5, 56.0, 54.0, 52.1, 40.6, 31.8, 30.8, 25.6, 24.6, 22.9, 21.8, 20.7, 19.7, 18.0, 17.8, 17.6, 15.4, −1.5, −4.3, −5.1, −5.2, −5.3; IR (film): $\tilde{\nu}=3443$, 3301, 2930, 1733, 1696, 1682, 1507, 1362, 1251, 1126, 837, 777 cm^{-1}; ES-MS: m/z: calcd for $C_{41}H_{80}N_4O_{10}Si_3Na$ $[M+Na]^+$: 895.51, found 895.7, 135; $[\alpha]_D^{25}=+1.58$ ($c=1.0$ in $CHCl_3$).

Troc-D-valine (44): TrocCl (7.20 mL, 52.2 mmol) was added to a 0 °C solution of D-valine (5.10 g, 43.5 mmol) and aqueous 2M NaOH (50 mL). The resulting solution was maintained at 0 °C for 1 h, at rt for 1.5 h, and then diluted with H_2O (100 mL) and Et_2O (100 mL). The layers were separated, the aqueous layer was extracted with Et_2O (2 × 100 mL), and the combined organic extracts were discarded. The aqueous layer was acidified with 1M HCl (100 mL) and extracted with EtOAc (3 × 100 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. The crude residue was purified by chromatography on silica gel (3:1 hexanes/Et_2O then 1:1 hexanes/Et_2O then 3:1 Et_2O/hexanes then Et_2O) to give **44** (8.96 g, 70%) as a colorless solid that was homogeneous by TLC analysis: m.p. 147–150 °C; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=11.5$ (br s, 1H), 6.25–6.33 (m, 0.3H), 5.51 (d, $J=9.1$ Hz, 0.7H), 4.83–4.67 (m, 2H), 4.37 (dd, $J=9.1$, 4.6 Hz, 0.7H), 4.35–4.30 (m, 0.3), 2.40–2.25 (m, 1H), 1.19–0.86 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=177.0$, 154.6, 95.3, 74.7, 59.0, 31.1, 19.0, 17.3; IR (film): $\tilde{\nu}=3431$, 3272, 3020, 1719, 1515, 1216, 1115, 756 cm^{-1}; ES-MS: m/z: calcd for $C_8H_{12}Cl_3NO_4Na$ $[M+Na]^+$: 393.97, found: 314.0; $[\alpha]_D^{25}=-4.11$ ($c=1.0$ in $CHCl_3$).



Pentadepsipeptide acid 45: IPCC (0.373 mL, 3.41 mmol) was added to a −50 °C solution of Troc-D-valine (**44**, 1.43 g, 4.87 mmol), TEA (0.476 mL, 3.41 mmol), DMAP (178 mg, 1.46 mmol), and CH_2Cl_2 (10 mL). After 3 min, a solution of **43** (850 mg, 0.975 mmol) and CH_2Cl_2 (5 mL) was added. The reaction mixture was allowed to come to rt over 6 h and then diluted with EtOAc (100 mL) and 1M HCl (20 mL). The layers were separated and organic layer was washed with 1M HCl (3 × 20 mL), saturated aqueous $NaHCO_3$ (2 × 30 mL), brine (1 × 20 mL), dried ($MgSO_4$), and concentrated. The crude residue was purified by chromatography on silica gel (8:1 hexanes/Et_2O then 3:1 hexanes/Et_2O then 1:1 hexanes/Et_2O then 3:1 Et_2O/hexanes) to give the fully protected pentadepsipeptide (953 mg, 85%) as a colorless oil that was homogeneous by TLC analysis: ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=8.34$ (br s, 1H), 6.76–6.69 (m, 1H), 5.88–5.79 (m, 1H), 5.53–5.41 (m, 1H), 5.27 (d, $J=17.1$ Hz, 1H), 5.19–5.10 (m, 2H), 4.90–4.22 (m, 11H), 4.00–3.74 (m, 2H), 3.66–3.33 (m, 1H), 2.42–1.95 (m, 5H), 1.81–1.55 (m, 2H), 1.09 (d, $J=6.2$ Hz, 3H), 0.97–0.75 (m, 41H), 0.006–−0.067 (m, 21H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=171.9$, 170.3, 169.8, 154.2, 131.5, 118.8, 95.3, 74.5, 68.8, 65.7, 64.5, 59.1, 57.5, 56.2, 52.0, 39.9, 31.2, 25.5, 24.3, 22.8, 21.8, 20.6, 19.0, 17.8, 17.7, 17.4, 17.1, −1.6, −4.4, −5.3; IR (film): $\tilde{\nu}=3441$, 3298, 2956, 1736, 1717, 1697, 1508, 1251, 1126, 838 cm^{-1}; ES-MS: m/z: calcd for $C_{49}H_{90}Cl_3N_5O_{13}Si_3Na$ $[M+Na]^+$: 1168.48, found: 1168.6, 135; $[\alpha]_D^{25}=+13.6$ ($c=1.0$ in $CHCl_3$).



A solution of $ZnCl_2$ (1M in Et_2O, 100 mL) was added to this pentadepsipeptide (4.00 g, 3.49 mmol) and CH_3NO_2 (10.0 mL). The Et_2O was evaporated with a stream of argon and the resulting solution was maintained at rt for 41 h. The reaction was diluted with EtOAc (200 mL) and quenched with 1M HCl (50 mL). The layers were separated and organic layer was washed with 1M HCl (3 × 50 mL), saturated aqueous $NaHCO_3$ (2 × 50 mL), brine (1 × 50 mL), dried (Na_2SO_4), and concentrated.

TBSOTf (6.40 mL, 27.9 mmol) was added to a −78 °C solution of the crude residue, lutidine (6.50 mL, 55.8 mmol), and CH_2Cl_2 (25 mL). The solution was maintained at −78 °C for 4 h, and then poured into a mixture of EtOAc (200 mL) and saturated aqueous $NaHCO_3$ (50 mL). The layers were separated and organic layer was washed with 1M HCl (3 × 50 mL), saturated aqueous $NaHCO_3$ (2 × 50 mL), brine (1 × 50 mL), dried ($MgSO_4$), and concentrated. The crude residue was purified by chromatography on silica gel (8:1 hexanes/Et_2O then 3:1 hexanes/Et_2O then 1:1 hexanes/Et_2O then 3:1 Et_2O/hexanes then Et_2O) to give the free piperazic NH-derivative (3.32 g, 95%) as a colorless oil that was homogeneous by

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TLC analysis: ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 6.88$ (d, $J = 9.3$ Hz, 1H), 6.81 (d, $J = 9.9$ Hz, 1H), 6.65 (d, $J = 9.6$ Hz, 1H), 5.95–5.87 (m, 1H), 5.67 (d, $J = 7.4$ Hz, 1H), 5.31 (d, $J = 17.2$ Hz, 1H), 5.23 (d, $J = 10.4$ Hz, 1H), 5.00 (d, $J = 6.6$ Hz, 1H), 4.92 (d, $J = 12.0$ Hz, 1H), 4.85–4.77 (m, 2H), 4.75–4.70 (m, 2H), 4.67 (dd, $J = 9.6$, 4.0 Hz, 1H), 4.64 (dd, $J = 12.9$, 6.2 Hz, 1H), 4.40–4.32 (m, 1H), 4.31 (d, $J = 12.0$ Hz, 1H), 3.83 (br s, 1H), 2.85–2.76 (m, 3H), 2.41–2.33 (m, 1H), 2.29–2.14 (m, 1H), 1.85–1.77 (m, 1H), 1.68–1.51 (m, 3H), 1.12 (d, $J = 6.2$ Hz, 3H), 1.05 (d, $J = 6.2$ Hz, 3H), 1.00 (d, $J = 6.7$ Hz, 3H), 0.99 (d, $J = 6.7$ Hz, 3H), 0.87 (t, $J = 7.1$ Hz, 6H), 0.82 (s, 9H), 0.78 (s, 9H), 0.070 (s, 3H), 0.0012 (s, 3H), −0.016 (s, 3H), −0.066 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 173.7$, 172.6, 171.3, 170.4, 168.1, 154.5, 131.3, 119.3, 95.5, 74.4, 69.3, 66.3, 62.2, 59.0, 57.3, 54.0, 52.5, 49.3, 43.2, 31.9, 30.2, 29.4, 25.9, 25.7, 24.5, 23.2, 21.6, 21.0, 19.1, 18.7, 18.6, 18.3, 17.8, 17.1, −4.5, −5.0, −5.2, −5.7; IR (film): $\tilde{\nu} = 3388$, 2958, 1735, 1717, 1672, 1509, 1470, 1375, 1160, 1101, 914, 836 cm^{-1}; ES-MS: *m*/*z*: calcd for $C_{43}H_{78}Cl_3N_5O_{11}Si_2Na$ $[M+Na]^+$: 1024.42, found: 1024.6, 135; $[\alpha]_D^{25} = +19.7$ ($c = 1.0$ in $CHCl_3$).

$PhSiH_3$ (0.810 mL, 6.58 mmol) was added to a 0 °C solution of this derivative (3.30 g, 3.29 mmol), $[Pd(Ph_3P)_4]$ (50 mg) and THF (20 mL). After 45 min, the reaction was quenched with H_2O (0.50 mL) and concentrated. The crude residue was purified by chromatography on silica gel (8:1 hexanes/Et_2O then 3:1 hexanes/Et_2O then 1:1 hexanes/Et_2O then 3:1 Et_2O/hexanes then Et_2O) to give **45** (2.71 g, 86%) as a colorless solid that was homogeneous by TLC analysis: m.p. 226–228 °C; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 6.87$ (d, $J = 7.3$ Hz, 1H), 6.82 (d, $J = 9.5$ Hz, 1H), 6.23 (d, $J = 9.4$ Hz, 1H), 5.69–5.66 (m, 1H), 4.99 (d, $J = 7.0$ Hz, 1H), 4.88 (d, $J = 12.0$ Hz, 1H), 4.84–4.62 (m, 2H), 4.61–4.59 (m, 1H), 4.52 (dd, $J = 9.5$, 4.4 Hz, 1H), 4.45 (d, $J = 12.0$ Hz, 1H), 4.45–4.38 (m, 1H), 3.83 (br s, 1H), 2.85–2.73 (m, 3H), 2.42–2.30 (m, 1H), 2.28–2.18 (m, 1H), 1.89–1.75 (m, 1H), 1.65–1.45 (m, 3H), 1.08 (d, $J = 6.2$ Hz, 3H), 1.04 (d, $J = 6.8$ Hz, 3H), 1.00–0.80 (m, 15H), 0.88 (s, 9H), 0.81 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H), 0.057 (s, 3H), 0.0064 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 173.5$, 172.5, 171.9, 171.3, 168.5, 154.5, 95.4, 74.6, 68.4, 62.1, 59.1, 57.1, 54.0, 52.3, 49.2, 42.7, 31.7, 30.4, 29.4, 25.9, 25.7, 24.5, 23.0, 21.8, 19.4, 19.0, 18.7, 18.4, 18.0, 17.8, 17.1, −4.8, −5.0, −5.1, −5.6; IR (film): $\tilde{\nu} = 3382$, 3019, 1733, 1671, 1515, 1255, 1215, 1103, 1036, 836 cm^{-1}; ES-MS: *m*/*z*: calcd for $C_{40}H_{74}Cl_3N_5O_{11}Si_2Na$ $[M+Na]^+$: 984.39, found: 984.5, 135; $[\alpha]_D^{25} = +19.8$ ($c = 1.0$ in $CHCl_3$).

***trans*-Hexadepsipeptide dimer 46**: HATU (489 mg, 1.29 mmol) was added to a −10 °C solution of **24** (240 mg, 0.322 mmol), **45** (1.24 g, 1.29 mmol), HOAt (350 mg, 2.57 mmol), collidine (0.51 mL, 3.86 mmol), and CH_2Cl_2 (5.0 mL). The reaction mixture was stirred at −10 °C for 19 h, 0 °C for 22 h, rt for 11 h and then quenched with 1M HCl (5 mL) and diluted with EtOAc (30 mL). The layers were separated and the organic layer was washed with 1M HCl (3 × 10 mL), saturated aqueous $NaHCO_3$ (3 × 10 mL), brine (1 × 10 mL), dried ($MgSO_4$), and concentrated. The crude residue was purified by chromatography on silica gel (8:1 hexanes/Et_2O then 3:1 hexanes/Et_2O then 1:1 Et_2O/hexanes then 3:1 Et_2O/hexanes then Et_2O then EtOAc) to yield **46** (565 mg, 67%) as a colorless oil that was homogeneous by TLC analysis: ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.90$–7.80 (m, 1H), 7.35–7.15 (m, 5H), 6.80–6.41 (m, 6H), 5.65–4.32 (m, 26H), 4.12–3.78 (m, 6H), 3.10–2.65 (m, 10H), 2.50–2.17 (m, 6H), 1.81–1.33 (m, 8H), 1.15–0.75 (m, 96H), 0.54–0.39 (m, 12H), 0.31–0.01 (m, 24H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 174.4$, 173.3, 171.4, 171.2, 171.0, 170.9, 170.8, 170.1, 169.7, 169.4, 169.3, 169.2, 169.1, 169.0, 168.3, 168.2, 168.1, 167.8, 166.7, 154.5, 154.4, 154.2, 154.1, 153.6, 153.5, 150.5, 150.4, 149.2, 149.0, 135.8, 135.0, 132.7, 132.2, 131.5, 131.4, 131.2, 129.2, 129.1, 129.0, 128.0, 127.9, 127.2, 127.1, 125.3, 123.0, 118.4, 118.2, 110.1, 109.8, 95.6, 95.1, 86.5, 86.4, 82.2, 82.1, 82.0, 76.5, 74.5, 74.3, 70.0, 69.8, 66.5, 66.2, 62.1, 62.0, 59.5, 59.4, 59.1, 56.6, 54.2, 54.0, 53.4, 52.4, 49.3, 49.2, 46.7, 46.1, 43.2, 43.0, 42.8, 42.6, 42.2, 32.5, 31.5, 30.3, 30.2, 29.5, 29.4, 26.0, 25.9, 25.8, 25.6, 25.5, 24.5, 24.3, 23.2, 22.9, 21.8, 21.6, 19.3, 19.1, 18.8, 18.7, 18.6, 18.4, 18.3, 18.2, 18.0, 17.9, 17.7, 17.5, 17.3, 16.6, 6.7, 6.6, 5.4, 5.3, −4.7, −4.8, −4.9, −5.0, −5.2, −5.3, −5.5, −5.6, −5.7, −5.8; IR (film): $\tilde{\nu} = 3381$, 2932, 1734, 1676, 1644, 1442, 1254, 1102, 834 cm^{-1}; ES-MS: *m*/*z*: calcd for $C_{120}H_{202}Cl_6N_{14}O_{26}Si_6Na$ $[M+Na]^+$: 2656.16, found: 2656.3, 135; $[\alpha]_D^{25} = -119$ ($c = 0.65$ in $CHCl_3$).

***trans*-Hexadepsipeptide carboxylic acid dimer 47**: $PhSiH_3$ (0.15 mL, 1.23 mmol) was added to a 0 °C solution of **46** (530 mg, 0.201 mmol), $[Pd(Ph_3P)_4]$ (20 mg) and THF (5 mL). The resulting solution was maintained at 0 °C for 45 min, warmed to rt for 15 min, quenched with H_2O (0.20 mL) and then concentrated. The crude residue was purified by chromatography on silica gel (8:1 hexanes/Et_2O then 3:1 hexanes/Et_2O then 1:1 Et_2O/hexanes then 3:1 Et_2O/hexanes then Et_2O then EtOAc) to give **47** (469 mg, 91%) as a colorless oil that was homogeneous by TLC analysis: ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.80$–6.41 (m, 12H), 5.80–5.52 (m, 2H), 5.35–4.38 (m, 16H), 4.10–3.79 (m, 4H), 3.08–2.17 (m, 16H), 1.82–1.20 (m, 8H), 1.18–0.75 (m, 96H), 0.55–0.31 (m, 12H), 0.28– −0.10 (m, 24H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 174.2$, 173.1, 171.3, 171.2, 170.3, 169.8, 168.2, 167.9, 154.5, 154.3, 153.6, 151.3, 134.1, 132.0, 128.5, 128.4, 128.0, 127.5, 127.0, 125.3, 110.5, 95.4, 95.1, 82.7, 76.4, 74.6, 74.5, 74.3, 69.6, 62.1, 59.2, 55.8, 54.0, 53.3, 49.2, 49.1, 42.8, 32.5, 31.7, 31.6, 31.4, 30.4, 30.2, 29.5, 29.4, 26.0, 25.8, 24.4, 24.1, 23.2, 22.7, 22.5, 22.1, 21.9, 21.6, 19.8, 19.3, 19.2, 19.0, 18.8, 18.6, 18.4, 18.3, 18.2, 17.9, 17.3, 17.1, 16.8, 6.7, 6.6, 5.7, 5.5, 5.4, −4.7, −4.8, −4.9, −5.0, −5.2, −5.5, −5.6; IR (film): $\tilde{\nu} = 3378$, 3302, 2956, 1731, 1675, 1642, 1253, 1217, 1116, 834 cm^{-1}; ES-MS: *m*/*z*: calcd for $C_{114}H_{194}Cl_6N_{14}O_{26}Si_6Na$ $[M+Na]^+$: 2576.09, found: 2576.4, 135; $[\alpha]_D^{25} = -94.5$ ($c = 0.65$ in $CHCl_3$).

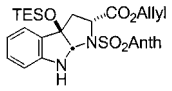
Isohimastatin (1): Pb/Cd couple (300 mg) was added to a vigorously stirred mixture of **47** (305 mg, 0.120 mmol), THF (5.0 mL), and aqueous 1M NH_4OAc (5.0 mL). After 1.5 h, the layers were separated, and the aqueous layer was extracted with EtOAc (4 × 5 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. This crude amino acid (250 mg, ≈95%) was split into two equal batches and used without further purification.

HATU (86.0 mg, 0.227 mmol) was added to a solution of the crude amino acid (≈125 mg), HOAt (62.0 mg, 0.454 mmol), iPr$_2$NEt (0.12 mL, 0.681 mmol), and DMF (40.0 mL) at rt. The resulting solution was maintained at rt for 28 h and then concentrated. The resulting crude residue was dissolved in EtOAc (10 mL) and washed with aqueous 1M HCl (3 × 5 mL), saturated aqueous $NaHCO_3$ (3 × 5 mL), brine (1 × 5 mL), dried (Na_2SO_4), and concentrated. The two batches of cyclic dimer **48** (≈145 mg each) were recombined at this stage and used without further purification.

A solution of TBAF (1M in THF, 3.40 mL) was added to a 0 °C solution of the crude residue **48** (≈290 mg), HOAc (0.583 mL, 10.2 mmol), and THF (3 mL). The resulting solution was allowed to warm to rt, maintained at rt for 55 h and then concentrated to a slurry. The reaction mixture was filtered through a short pad of sand and washed with CH_2Cl_2 (200 mL). The filtrate was discarded. The remaining white solid was washed with hot MeOH (250 mL) until all the solid had dissolved and the filtrate was concentrated to give **1** (85.4 mg, 48%) as a white solid that was >95% pure as judged by ^{13}C NMR analysis: m.p. >400 °C (dec); ^{1}H NMR (500 MHz, [D$_6$]DMSO): $\delta = 8.24$ (d, $J = 8.4$ Hz, 2H), 7.68 (d, $J = 8.1$ Hz, 2H), 7.35 (s, 2H), 7.20–7.15 (m, 4H), 7.00 (d, $J = 4.2$ Hz, 2H), 6.54 (d, $J = 8.2$ Hz, 2H), 5.94 (s, 2H), 5.75 (d, $J = 7.3$ Hz, 2H), 5.52 (d, $J = 4.3$ Hz, 2H), 5.45 (d, $J = 6.0$ Hz, 2H), 5.29 (d, $J = 5.2$ Hz, 2H), 5.20 (d, $J = 11.8$ Hz, 2H), 4.98–4.90 (m, 4H), 4.61 (dd, $J = 8.4$, 4.3 Hz, 2H), 4.55–4.48 (m, 2H), 4.30 (dd, $J = 8.8$, 4.0 Hz, 2H), 3.90–3.82 (m, 2H), 3.60–3.50 (m, 2H), 2.90–2.75 (m, 3H), 2.49 (d, $J = 13.2$ Hz, 2H), 2.06–1.90 (m, 6H), 1.71–1.60 (m, 2H), 1.60–1.51 (m, 2H), 1.49–1.39 (m, 2H), 1.05 (d, $J = 6.3$ Hz, 6H), 0.95–0.80 (m, 24H), 0.39 (d, $J = 6.9$ Hz, 6H), 0.23 (d, $J = 6.9$ Hz, 6H); ^{13}C NMR (125 MHz, DMSO): $\delta = 170.6$, 170.4, 170.3, 169.9, 169.2, 147.9, 132.2, 127.1, 121.2, 110.8, 86.0, 84.0, 75.1, 67.3, 61.8, 58.9, 55.6, 53.7, 52.7, 50.8, 49.6, 43.8, 42.3, 31.7, 29.1, 28.8,

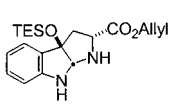
24.1, 23.1, 22.3, 18.7, 18.6, 17.7, 17.4, 17.3; IR (film): $\tilde{\nu}$ = 2957, 2931, 2857, 1689, 1253, 1100, 1083 cm^{-1}; ES-MS: *m*/*z*: calcd for $C_{72}H_{104}N_{14}O_{20}Na$ $[M+Na]^+$: 1507.74, found: 1508.1, 135.

Allyl ester 49: Neat TESOTf (10.4 mL, 45.1 mmol) was added to a 0 °C solution of **11** (2.60 g, 50.4 mmol), 2,6-lutidine (10.5 mL, 90.3 mmol), and CH_2Cl_2 (20 mL). The resulting solution was allowed to warm to rt overnight and then quenched with saturated aqueous $NaHCO_3$ (100 mL) and diluted with EtOAc (100 mL). The layers were separated and the organic layer was washed with aqueous 1M HCl (2 × 50 mL), brine (1 × 50 mL), dried (Na_2SO_4), and concentrated.

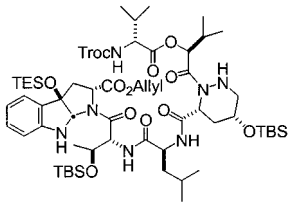


EDCI (1.70 g, 8.90 mmol) was added to a 0 °C solution of the crude residue, allyl alcohol (31.0 mL, 451 mmol), DMAP (20 mg), and CH_2Cl_2 (50 mL). The resulting solution was allowed to warm to rt overnight and then concentrated. The crude residue was purified by chromatography on silica gel (8:1 hexanes/Et_2O then 3:1 hexanes/Et_2O then 1:1 Et_2O/hexanes then 3:1 Et_2O/hexanes then Et_2O) to give **49** (2.40 g, 78%) as a yellow solid that was homogeneous by TLC analysis: m.p. 112–114 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.41 (d, *J* = 9.3 Hz, 2H), 8.71 (s, 1H), 8.03 (d, *J* = 8.4 Hz, 2H), 7.74–7.62 (m, 2H), 7.53 (t, *J* = 7.5 Hz, 2H), 7.10–7.01 (m, 1H), 6.69 (t, *J* = 7.4 Hz, 1H), 6.51 (t, *J* = 8.2 Hz, 1H), 5.45–5.31 (m, 1H), 5.12–5.01 (m, 2H), 4.98 (s, 1H), 4.91 (d, *J* = 7.8 Hz, 1H), 4.75 (s, 1H), 3.98 (dd, *J* = 13.0, 5.7 Hz, 1H), 3.80 (dd, *J* = 13.0, 5.8 Hz, 1H), 2.78 (d, *J* = 12.6 Hz, 1H), 2.53 (dd, *J* = 12.6, 9.0 Hz), 0.56 (t, *J* = 7.9 Hz, 9H), 0.20–0.08 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.0, 150.1, 136.5, 131.3, 131.2, 130.6, 129.5, 129.1, 128.2, 127.6, 125.4, 125.0, 124.5, 119.1, 118.2, 110.3, 89.3, 82.6, 66.0, 61.0, 43.4, 6.4, 5.1; IR (film): $\tilde{\nu}$ = 3408, 3020, 2956, 1727, 1612, 1216, 1162, 908 cm^{-1}; MS: *m*/*z*: calcd for $C_{34}H_{38}N_2O_5SSiNa$ $[M+Na]^+$: 637.22, found: 637.3, 135; $[\alpha]_D^{25}$ = −156 (*c* = 1.0 in $CHCl_3$).

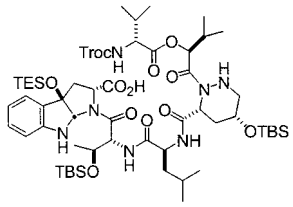
Pyrroloindoline 50: Freshly prepared Al(Hg) (1.0 g) was added to a vigorously stirred mixture of **49** (2.90 g, 4.72 mmol) and THF/H_2O 10:1 (200 mL) at 0 °C. The resulting mixture turned from bright yellow to gray over 1 h indicating consumption of **49**. The mixture was filtered through a pad of celite (EtOAc) and concentrated. The crude residue was purified by chromatography on silica gel (8:1 hexanes/Et_2O then 3:1 hexanes/Et_2O then 1:1 Et_2O/hexanes then 3:1 Et_2O/hexanes then Et_2O then EtOAc) to give **50** (1.17 g, 69%) as a near colorless oil that was homogeneous by TLC analysis: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.20 (d, *J* = 8.1 Hz, 1H), 7.11 (dt, *J* = 7.5, 1.2 Hz, 1H), 6.73 (dt, *J* = 7.4, 0.7 Hz, 1H), 6.57 (d, *J* = 7.9 Hz, 1H), 5.75–5.60 (m, 1H), 5.25–5.10 (m, 2H), 4.86 (s, 1H), 4.35–4.22 (m, 2H), 4.03 (dd, *J* = 7.3, 5.3 Hz, 1H), 2.67 (dd, *J* = 12.7, 7.4 Hz, 1H), 2.50 (dd, *J* = 12.7, 5.3 Hz, 1H), 0.83 (t, *J* = 3.3 Hz, 9H), 0.50–0.30 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.9, 149.4, 131.7, 130.5, 129.6, 124.4, 118.5, 118.1, 110.1, 90.0, 84.4, 65.3, 59.4, 44.5, 6.6, 5.5; IR (film): $\tilde{\nu}$ = 3368, 2875, 1737, 1612, 1470, 1203, 1008 cm^{-1}; ES-MS: *m*/*z*: calcd for $C_{20}H_{31}N_2O_3Si$ $[M+H]^+$: 375.20, found: 375.2, 135; $[\alpha]_D^{25}$ = −70.3 (*c* = 1.0 in $CHCl_3$).



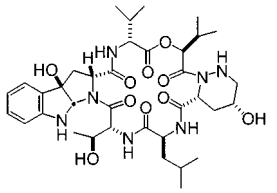
***trans*-Hexadepsipeptide monomer 51**: The same procedure for the preparation of **46** was used with the following amounts: HATU (198 mg, 0.52 mmol), **50** (195 mg, 0.52 mmol), acid **45** (250 mg, 0.26 mmol), HOAt (141 mg, 1.04 mmol), collidine (273 μL, 2.08 mmol), and CH_2Cl_2 (3.0 mL) to give **51** (224 mg, 66%) as a colorless oil that was homogeneous by TLC analysis: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.80–7.00 (m, 3H), 6.80–6.41 (m, 4H), 5.71–5.40 (m, 2H), 5.38–4.35 (m, 11H), 4.10–3.90 (m, 2H), 3.85 (br s, 1H), 3.05–2.62 (m, 5H), 2.41–2.16 (m, 2H), 1.78–1.35 (m, 4H), 1.18–0.75 (m, 48H), 0.46–0.31 (m, 6H), 0.25–0.20 (m, 12H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.5, 173.4, 171.4, 171.2, 171.1, 170.9, 170.8, 170.0, 169.7, 169.3, 169.1, 168.2, 168.1, 167.9, 166.8, 154.6, 153.6, 151.7, 150.5, 131.6, 131.5, 131.4, 130.6, 127.4, 126.7, 124.9, 124.8, 118.6, 118.4, 118.3, 117.7, 109.9, 109.6, 95.6, 95.2, 86.5, 86.4, 81.8, 81.7, 76.5, 75.8, 74.5, 74.3, 70.1, 69.8, 66.6, 66.3, 62.2, 62.1, 59.5, 59.3, 59.2, 59.1, 56.6, 55.8, 54.1, 54.0, 53.4, 52.5, 52.4, 49.3, 49.2, 43.0, 42.9, 42.7, 42.5, 32.6, 31.5, 31.3, 30.4, 30.3, 29.6, 29.4, 26.0, 25.9, 25.8, 25.5, 24.5, 24.4, 23.2, 23.0, 22.5, 21.8, 21.7, 19.4, 19.3, 19.2, 18.8, 18.7, 18.6, 18.5, 18.3, 18.2, 18.0, 17.4, 16.7, 6.7, 6.6, 5.6, 5.4, 5.3, −4.7, −4.8, −4.9, −5.0, −5.1, −5.4, −5.5, −5.6; IR (film): $\tilde{\nu}$ = 3382, 2956, 1733, 1676, 1642, 1255, 1039, 1004, 755 cm^{-1}; ES-MS: *m*/*z*: calcd for $C_{60}H_{102}Cl_3N_7O_{13}Si_3Na$ $[M+Na]^+$: 1340.58, found: 1340.8, 135; $[\alpha]_D^{25}$ = −86.6 (*c* = 0.65, $CHCl_3$).



***trans*-Hexadepsipeptide carboxylic acid monomer 52**: The same procedure for the preparation of **47** was used with the following amounts: $PhSiH_3$ (36.0 μL, 0.295 mmol), **51** (195 mg, 0.148 mmol), $[Pd(Ph_3P)_4]$ (20 mg), and THF (3.0 mL) to give **52** (174 mg, 92%) as a colorless oil that was homogeneous by TLC analysis: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.75–6.39 (m, 7H), 5.70–5.58 (m, 1H), 5.22–4.37 (m, 10H), 4.16–3.60 (m, 2H), 3.15–2.15 (m, 7H), 1.80–1.30 (m, 4H), 1.16–0.71 (m, 48H), 0.45–0.30 (m, 6H), 0.29–0.01 (m, 12H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.2, 173.7, 172.3, 172.0, 171.7, 171.5, 171.3, 171.2, 170.1, 169.9, 168.7, 168.3, 166.9, 135.0, 134.3, 132.0, 131.0, 130.7, 128.4, 127.5, 127.4, 125.4, 124.4, 118.3, 117.6, 110.2, 109.9, 95.5, 95.4, 95.2, 87.2, 86.8, 82.0, 81.9, 76.4, 75.8, 74.8, 74.6, 74.4, 69.7, 69.1, 62.3, 59.5, 59.2, 59.1, 55.7, 53.8, 53.2, 52.5, 49.3, 49.2, 46.8, 43.4, 42.9, 42.4, 32.7, 31.6, 31.3, 30.5, 30.2, 29.6, 29.5, 26.0, 25.9, 25.8, 25.5, 24.4, 24.2, 23.4, 23.0, 21.9, 20.0, 19.5, 19.0, 18.7, 18.6, 18.3, 18.0, 17.7, 17.6, 17.1, −4.6, −4.7, −4.9, −5.0, −5.6; IR (film): $\tilde{\nu}$ = 3379, 3298, 2956, 1735, 1675, 1642, 1253, 1108, 1038, 756 cm^{-1}; ES-MS: *m*/*z*: calcd for $C_{57}H_{98}Cl_3N_7O_{13}Si_3Na$ $[M+Na]^+$: 1300.55, found: 1300.7, 135; $[\alpha]_D^{25}$ = −76.4 (*c* = 0.4 in $CHCl_3$).

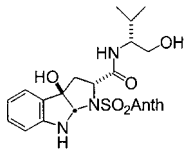


***trans*-Cyclic monomer 3**: The same procedure for the preparation of **1** was used with the following amounts: Pb/Cd couple (100 mg), **52** (158 mg, 0.12 mmol), THF (3.0 mL), aqueous 1M NH_4OAc (3.0 mL); HATU (11.0 mg, 0.029 mmol), the crude amino acid (≈120 mg), HOAt (45.0 mg, 0.327 mmol), iPr_2NEt (57.0 μL, 0.327 mmol), and DMF (75.0 mL); TBAF (1M in THF, 1.44 mL), the crude cyclic monomer (≈130 mg), HOAc (0.24 mL, 4.52 mmol), and THF (1.0 mL) to give **3** (76.6 mg, 76%) as a colorless solid that was homogeneous by TLC analysis: m.p. >320 °C (dec); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.50 (br s, 1H), 7.40–7.20 (m, 2H), 7.01 (t, *J* = 7.6 Hz, 1H), 6.74 (t, *J* = 7.4 Hz, 1H), 6.55 (br s, 1H), 6.45 (d, *J* = 7.8 Hz, 1H), 5.84 (br s, 1H), 5.77 (s, 1H), 5.45 (d, *J* = 4.8 Hz, 1H), 5.17 (d, *J* = 10.0 Hz, 1H), 4.86 (d, *J* = 5.7 Hz, 1H), 4.74 (dd, *J* = 9.0, 3.0 Hz, 1H), 4.74–4.58 (m, 3H), 4.52 (s, 1H), 4.33 (d, *J* = 12.3 Hz, 1H), 4.28 (s, 1H), 3.63 (s, 1H), 3.15–3.00 (m, 1H), 2.72 (d, *J* = 14.0 Hz, 1H), 2.60 (t, *J* = 13.5 Hz, 1H), 2.60–2.55 (m, 1H), 2.14 (d, *J* = 14.7 Hz, 1H), 2.08–1.97 (m, 1H), 1.95–1.81 (m, 1H), 1.80–1.72 (m, 1H), 1.70–1.58 (m, 3H), 1.23 (d, *J* = 6.2 Hz, 3H), 1.00–0.95 (m, 9H), 0.90 (d, *J* = 6.2 Hz, 3H), 0.51 (d, *J* = 6.5 Hz, 3H), 0.28 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.8, 171.7, 171.3, 171.0, 170.9, 170.5, 148.2, 131.6, 129.7, 124.4, 120.4, 111.1, 86.6, 84.9, 75.9, 68.0, 62.2, 58.8, 56.5, 55.7, 53.1, 52.4, 50.0, 43.6, 32.1, 29.4, 28.6, 24.9, 23.0, 22.7, 19.3, 18.8, 18.1, 17.4, 17.1; IR (film): $\tilde{\nu}$ = 3324, 2963, 1736, 1653, 1526, 1428, 1204, 1100 cm^{-1}; ES-MS: *m*/*z*: calcd for $C_{36}H_{53}N_7O_{10}Na$ $[M+Na]^+$: 766.38, found: 766.5, 135; $[\alpha]_D^{25}$ = −48.3 (*c* = 1.0 in $CHCl_3$).



***trans*-Pyrroloindoline-D-valinol**: *tert*-Butyl ester **11** (110 mg, 0.213 mmol) was added to TFA (1.50 mL) at 0 °C. The reaction was maintained at 0 °C for 30 min, at rt for 3 h and concentrated.

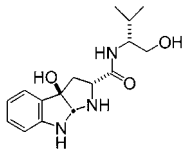
EDCI (82.0 mg, 0.430 mmol) was added to a 0 °C solution of this crude residue, D-valinol (66.0 mg, 0.640 mmol), DMAP (10 mg), and CH_2Cl_2 (10 mL). The reaction was allowed to warm to rt overnight and then concentrated. The crude residue was taken up in EtOAc (100 mL) and washed with 1M HCl (2 × 50 mL), saturated aqueous $NaHCO_3$ (1 × 50 mL), brine (1 × 50 mL), dried ($MgSO_4$), and concentrated. The crude residue was purified by chromatography on silica gel (8:1 hexanes/Et_2O then 3:1 hexanes/Et_2O then 1:1 Et_2O/hexanes then 3:1 Et_2O/hexanes then Et_2O then EtOAc) to give the



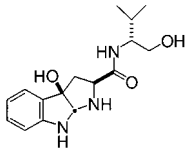
0947-6539/01/0701-0058 $ 17.50+.50/0 *Chem. Eur. J.* **2001**, *7*, No. 1

title compound (58.0 mg, 50%) as a pale yellow solid that was homogeneous by TLC analysis: m.p. 201–204 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.25 (d, J = 9.2 Hz, 2H), 8.72 (s, 1H), 8.01 (d, J = 8.3 Hz, 2H), 7.69–7.66 (m, 2H), 7.52–7.49 (m, 2H), 7.13 (d, J = 7.36 Hz, 1H), 7.08–7.06 (m, 1H), 6.80 (d, J = 8.5 Hz, 1H), 6.73 (t, J = 7.4 Hz, 1H), 6.60 (d, J = 8.0 Hz, 1H), 5.59 (s, 1H), 5.26 (s, 1H), 4.39 (dd, J = 9.9, 0.2 Hz, 2H), 3.09–3.03 (m, 2H), 3.03 (s, 1H), 3.00–2.92 (m, 1H), 2.74 (d, J = 13.4 Hz, 1H), 2.48–2.44 (m, 2H), 1.24–1.20 (m, 1H), 0.48 (d, J = 6.8 Hz, 3H), 0.33 (d, J = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.9, 148.2, 137.4, 131.3, 131.2, 130.8, 129.8, 129.4, 125.6, 125.5, 124.4, 124.2, 120.8, 110.9, 88.0, 85.3, 62.9, 62.8, 57.6, 41.2, 28.6, 18.7, 18.5; IR (film): $\tilde{\nu}$ = 3382, 3278, 3018, 1652, 1216, 909, 756 cm^{-1}; ES-MS: m/z:calcd for $C_{30}H_{31}N_3O_5SNa$ $[M+Na]^+$: 568.19, found: 568.1; $[\alpha]_D^{25} = -69.9$ (c = 1.0 in $CHCl_3$).

***trans*-Degradation product (53)**: Freshly prepared Al(Hg) (500 mg) was added to a vigorously stirred mixture of the sulfonylated dipeptide (58.0 g, 0.107 mmol) and THF/H_2O 10:1 (20 mL) at 0 °C. The resulting mixture turned from bright yellow to gray over 1 h indicating consumption of starting material. The mixture was filtered through a pad of celite (EtOAc) and concentrated. The crude residue was purified by chromatography on silica gel (3:1 hexanes/Et_2O then 3:1 Et_2O/hexanes then Et_2O then EtOAc then 1:1 EtOAc/MeOH) to give **53** (15 mg, 50%) as a pale yellow solid. Further purification by chromatography on silica gel (Et_2O then CH_2Cl_2 then 8:1 $CHCl_3$/MeOH then 4:1 $CHCl_3$/MeOH then MeOH) gave **53** (10.0 mg, 31%) as a colorless solid that was homogeneous by TLC analysis: m.p. >310 °C (dec); ^{1}H NMR (500 MHz, MeOH): δ = 7.12 (dd, J = 7.4, 0.7 Hz, 1H), 6.96 (dt, J = 7.7, 1.16 Hz, 1H), 6.64 (dt, J = 7.4, 0.6 Hz, 1H), 6.52 (d, J = 7.9 Hz, 1H), 4.93 (s, 1H), 4.00 (dd, J = 8.8, 6.5 Hz, 1H), 3.43–3.41 (m, 3H), 2.57 (dd, J = 13.4, 8.9 Hz, 1H), 2.15 (dd, J = 13.5, 6.5 Hz, 1H), 1.60–1.58 (m, 1H), 0.66 (d, J = 6.8 Hz, 3H), 0.0.57 (d, J = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, MeOH): δ = 177.2, 150.4, 133.3, 130.6, 124.6, 120.2, 111.8, 90.5, 88.5, 63.4, 63.2, 57.6, 45.4, 30.2, 19.9, 18.7; IR (film): $\tilde{\nu}$ = 3352, 2944, 1642, 1467, 1117, 1027 cm^{-1}; ES-MS: m/z: calcd for $C_{16}H_{23}N_3O_3Na$ $[M+Na]^+$: 328.16, found: 328.1, 135; $[\alpha]_D^{25} = -2.97$ (c = 0.35 in MeOH).



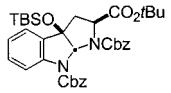
***cis*-Degradation product 54**: Neat TMSOTf (0.760 mL, 3.94 mmol) was added to a 0 °C solution of **14** (100 mg, 0.197 mmol), 2,6-lutidine (1.40 mL, 11.8 mmol), and CH_2Cl_2 (3 mL). The resulting solution was allowed to warm to rt over 4 h and then quenched with saturated aqueous $NaHCO_3$ (50 mL) and diluted with EtOAc (100 mL). The layers were separated and the organic layer was washed with aqueous 1M HCl (3 × 50 mL), brine (1 × 50 mL), dried (Na_2SO_4), and concentrated.



EDCI (76.0 mg, 0.396 mmol) was added to a 0 °C solution of this crude residue, D-valinol (61.0 mg, 0.592 mmol), DMAP (10 mg), and CH_2Cl_2 (3 mL). The reaction was allowed to warm to rt overnight and then concentrated. The crude residue was purified by chromatography on silica gel (8:1 hexanes/Et_2O then 1:1 hexanes/Et_2O then Et_2O then EtOAc) to give a mixture of the 3a-OH and the 3a-OTMS ether (50 mg) as a near colorless oil which was used without further purification.

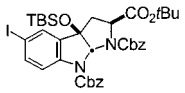
Piperidine (19.0 μL, 0.190 mmol) was added to a 0 °C solution of this mixture (50 mg) and CH_3CN (2 mL). The resulting solution was allowed to warm to rt over 3 h and then concentrated. TFA (1.0 mL) was added to a 0 °C solution of this residue and CH_2Cl_2 (1.0 mL). After 10 min, the reaction was concentrated and the crude residue was purified by chromatography on TEA treated silica gel (3:1 Et_2O/hexanes then Et_2O then EtOAc then 3:1 EtOAc/MeOH) to give **54** (30 mg, 50%) as a colorless solid that was homogeneous by TLC analysis: m.p. >250 °C (dec); ^{1}H NMR (500 MHz, MeOH): δ = 7.25 (d, J = 7.1 Hz, 1H), 7.09 (dt, J = 7.8, 1.10 Hz, 1H), 6.76 (dt, J = 7.4, 0.5 Hz, 1H), 6.62 (d, J = 7.9 Hz, 1H), 5.06 (s, 1H), 3.73 (dd, J = 11.2, 5.9 Hz, 1H), 3.67–3.65 (m, 1H), 3.55 (dd, J = 11.4, 4.4 Hz, 1H), 3.48 (dd, J = 11.3, 6.4 Hz, 1H), 3.31 (s, 3H), 2.62 (dd, 12.4, 6.0 Hz, 1H), 2.30 (t, J = 11.8 Hz, 1H), 1.82–1.81 (m, 1H), 0.90 (d, J = 6.8 Hz, 3H), 0.0.85 (d, J = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, MeOH): δ = 172.6, 151.5, 131.9, 131.2, 125.2, 120.6, 111.2, 90.0, 85.7, 63.1, 60.8, 58.0, 46.1, 30.0, 20.1, 18.7; IR (film): $\tilde{\nu}$ = 3300, 2964, 1673, 1566, 1203, 1137, 1027 cm^{-1}; ES-MS: m/z: calcd for $C_{16}H_{23}N_3O_3Na$ $[M+Na]^+$: 328.16, found: 328.1, 135; $[\alpha]_D^{25}$ = −59.0 (c = 0.5 in MeOH).

Pyrroloindoline *tert*-butyl ester 56: Neat pyridine (9.30 mL, 116 mmol) was added to a 0 °C solution of **14** (4.00 g, 14.5 mmol), $ClCO_2Bn$ (8.20 mL, 58.0 mmol), and CH_2Cl_2 (100 mL). The resulting solution was allowed to warm to rt overnight and then concentrated. The crude residue was dissolved in EtOAc (100 mL) and washed with 1M HCl (2 × 50 mL), brine (1 × 50 mL), dried ($MgSO_4$), and concentrated. This residue was purified by chromatography on silica gel (8:1 hexanes/Et_2O then 3:1 hexanes/Et_2O then 1:1 Et_2O/hexanes then 3:1 Et_2O/hexanes then Et_2O) to give the bis-carbamate (5.00 g, 63%) as a near colorless oil that was homogeneous by TLC analysis: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.63 (br s, 1H), 7.36 (d, J = 7.4 Hz, 1H), 7.29–7.16 (m, 11H), 7.08 (t, J = 7.4 Hz, 1H), 6.08 (s, 1H), 5.21–4.43 (m, 4H), 3.96 (br s, 1H), 3.75 (s, 1H), 2.77 (dd, J = 12.9, 7.7 Hz, 1H), 2.40 (dd, J = 12.9, 9.1 Hz, 1H), 1.46 (br s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.0, 153.9, 153.3, 141.4, 135.8, 135.6, 132.2, 130.5, 128.5, 128.3, 128.2, 128.0, 127.9, 124.1, 123.1, 117.4, 83.7, 81.9, 81.4, 67.6, 67.2, 59.9, 37.5, 27.6; IR (film): $\tilde{\nu}$ = 3426, 2978, 1720, 1395, 1323, 1152, 1079, 735 cm^{-1}; ES-MS: m/z: calcd for $C_{31}H_{32}N_2O_7Na$ $[M+Na]^+$: 567.21, found: 567.3; $[\alpha]_D^{25} = -79.9$ (c = 1.0 in $CHCl_3$).

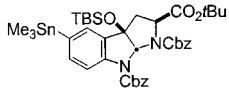


A solution of DBU (10.0 mL, 66.2 mmol) and DMF (50 mL) was added to a solution of the bis-carbamate (9.00 g, 16.5 mmol), TBSCl (14.8 g, 99.2 mmol), and DMF (300 mL). The resulting solution was maintained at rt for 8 h, and was then diluted with EtOAc (400 mL) and poured into aqueous 1M HCl (200 mL). The layers were separated and the organic layer was washed with aqueous 1M HCl (3 × 100 mL), saturated aqueous $NaHCO_3$ (1 × 100 mL), brine (2 × 100 mL), dried ($MgSO_4$), and concentrated. The crude residue was purified by chromatography on silica gel (3:1 hexanes/Et_2O then 1:1 Et_2O/hexanes then 3:1 Et_2O/hexanes) to give **56** (10.6 g, 97%) as a colorless oil that was homogeneous by TLC analysis: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.71 (br s, 1H), 7.38–7.22 (m, 12H), 7.12 (t, J = 7.4 Hz, 1H), 6.00 (br s, 1H), 5.40–4.40 (m, 4H), 3.89 (br s, 1H), 2.87 (dd, J = 12.3, 7.1 Hz, 1H), 2.41 (t, J = 12.2 Hz, 1H), 1.60–1.22 (br m, 9H), 0.74 (s, 9H), −0.29– −0.50 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.6, 154.4, 153.1, 142.4, 136.0, 132.1, 130.6, 128.3, 128.2, 128.0, 123.9, 118.0, 85.2, 81.5, 81.0, 67.4, 59.6, 38.5, 27.8, 25.3, 17.7, −3.9, −4.4; IR (film): $\tilde{\nu}$ = 3032, 2953, 2856, 1717, 1479, 1285, 1151, 837 cm^{-1}; ES-MS: m/z: calcd for $C_{37}H_{46}N_2O_7SiNa$ $[M+Na]^+$: 681.30, found: 681.6, 135; $[\alpha]_D^{25} = -64.2$ (c = 1.0 in $CHCl_3$).

5-Iodo-pyrroloindoline *tert*-butyl ester 57: The same procedure for the preparation of **17** was used with the following amounts: ICl (1.50 mL, 30.4 mmol), **56** (2.00 g, 3.04 mmol), 2,6-di-*tert*-butyl-4-methyl pyridine (6.23 g, 30.4 mmol), and CH_2Cl_2 (20 mL). The crude residue was purified by chromatography on silica gel (8:1 hexanes/Et_2O then 3:1 hexanes/Et_2O then 1:1 Et_2O/hexanes) to give **57** (1.75 g, 73%) as a light yellow foam that was homogeneous by TLC analysis: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.65 (d, J = 7.2 Hz, 1H), 7.62 (s, 1H), 7.48–7.03 (m, 11H), 5.97 (br s, 1H), 5.50–4.40 (m, 4H), 3.92 (br s, 1H), 2.81 (dd, J = 12.4, 7.2 Hz, 1H), 2.38 (dd, J = 12.4, 10.3 Hz, 1H), 1.62–1.24 (br m, 9H), 0.74 (s, 9H), −0.32– −0.45 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.4, 154.3, 152.9, 142.1, 139.3, 135.8, 134.8, 132.8, 128.3, 128.2, 128.0, 119.9, 86.3, 84.9, 81.6, 80.8, 67.4, 59.3, 38.3, 27.7, 25.3, 17.6, −3.8, −4.3; IR (film): $\tilde{\nu}$ = 2954, 2856, 1723, 1472, 1289, 1153, 1080, 1027, 838 cm^{-1}; ES-MS: m/z: calcd for $C_{37}H_{45}N_2O_7SiINa$ $[M+H]^+$: 807.19, found: 807.4, 135; $[\alpha]_D^{25} = -80.4$ (c = 1.0 in $CHCl_3$).



5-Trimethylstannyl-pyrroloindoline *tert*-butyl ester 58: The same procedure for the preparation of **18** was used with the following amounts: Me_6Sn_2 (2.10 mL, 6.30 mmol), **57** (2.50 g, 3.19 mmol), $[Pd(Ph_3P)_4]$ (0.37 g, 0.32 mmol) and THF (10 mL). The crude residue was purified by chromatography on silica gel (8:1 hexanes/Et_2O then 3:1 hexanes/Et_2O then 1:1 Et_2O/hexanes then 3:1 Et_2O/hexanes) to give **58** (2.27 g, 87%) as a light yellow foam that was homogeneous by TLC analysis: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.71 (br s, 1H), 7.51 (d, J = 7.9 Hz, 1H), 7.48 (s, 1H), 7.46–7.18 (m, 10H), 5.98 (br s, 1H), 5.50–4.40 (m,



4H), 3.92 (brs, 1H), 2.89 (dd, $J=12.3$, 7.2 Hz, 1H), 2.40 (dd, $J=12.4$, 7.3 Hz, 1H), 1.60–1.30 (brm, 9H), 0.74 (s, 9H), 0.31 (s, 9H), −0.32 to −0.50 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=170.8$, 153.1, 142.7, 137.9, 136.0, 131.8, 131.1, 128.3, 128.2, 128.0, 117.6, 85.4, 81.6, 80.9, 67.3, 59.6, 38.4, 27.8, 25.3, 17.7, −3.8, −4.4, −9.5; IR (film): $\tilde{\nu}=2953$, 2930, 1723, 1477, 1419, 1321, 1261, 1107 cm^{-1}; ES-MS: *m/z*: calcd for $C_{40}H_{54}N_2O_7SiSnNa$ $[M+Na]^+$: 843.26, found: 845.5, 135; $[\alpha]_D^{25}=-108$ ($c=1.0$ in $CHCl_3$).

Pyrroloindoline *tert*-butyl ester dimer 59: The same procedure for the preparation of **19** was used with the following amounts: **58** (2.10 g, 2.56 mmol) in DMF (8.0 mL), **57** (2.00 g, 2.56 mmol), $[Pd_2dba_3]$ (0.25 g, 0.26 mmol), Ph_3As (0.16 g, 0.51 mmol), and DMF (7.0 mL). The crude residue was purified by chromatography on silica gel (8:1 hexanes/Et_2O then 3:1 hexanes/Et_2O then 1:1 Et_2O/hexanes then 3:1 Et_2O/hexanes) to give **59** (2.77 g, 83%) as a pale yellow foam that was homogeneous by TLC analysis: ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=7.78$ (brs, 2H), 7.52 (d, $J=8.0$ Hz, 2H), 7.44 (s, 2H), 7.40–7.21 (m, 20H), 6.05 (brs, 2H), 5.40–4.50 (m, 8H), 3.96 (brs, 2H), 2.91 (dd, $J=$ 12.2, 7.2 Hz, 2H), 2.45 (m, 2H), 1.60–1.26 (brm, 18H), 0.77 (s, 18H), −0.31– −0.40 (m, 12H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=170.6$, 154.4, 153.1, 141.7, 136.9, 136.0, 132.9, 129.4, 128.3, 128.1, 127.7, 122.7, 118.2, 85.3, 81.7, 81.2, 67.4, 59.6, 38.5, 27.8, 25.3, 17.7, −3.7, −4.2; IR (film): $\tilde{\nu}=2954$, 2856, 1720, 1477, 1289, 1151, 1024 cm^{-1}; ES-MS: *m/z*: calcd for $C_{74}H_{90}N_4O_{14}Si_2Na$ $[M+Na]^+$: 1337.59, found: 1338.8, 135; $[\alpha]_D^{25}=-124$ ($c=1.0$ in $CHCl_3$).

3a-Hydroxypyrroloindoline *tert*-butyl ester dimer 60: The same procedure for the preparation of **20** was used with the following amounts: TBAF (1M in THF, 5.50 mL), **59** (3.60 g, 2.74 mmol), and THF (20 mL). The crude residue was purified by chromatography on silica gel (8:1 hexanes/Et_2O then 3:1 hexanes/Et_2O then 1:1 Et_2O/hexanes then 3:1 Et_2O/hexanes then Et_2O then EtOAc) to give the tertiary alcohol (2.78 g, 96%) as a light tan solid that was homogeneous by TLC analysis: m.p. >250 °C (dec); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=7.57$ (brs, 2H), 7.47 (s, 2H), 7.41 (d, $J=8.3$ Hz, 2H), 7.38–7.16 (m, 20H), 6.09 (s, 2H), 5.38–4.60 (m, 8H), 4.08 (brs, 2H), 3.97 (brs, 2H), 2.78 (dd, $J=13.0$, 7.8 Hz, 2H), 2.40 (dd, $J=12.9$, 8.8 Hz, 2H), 1.37 (brs, 18H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=171.3$, 153.5, 140.5, 135.9, 135.5, 133.0, 129.1, 128.4, 128.3, 128.1, 128.0, 121.5, 117.5, 83.8, 82.1, 67.9, 67.3, 60.0, 37.8, 27.7; IR (film): $\tilde{\nu}=3409$, 2977, 1719, 1478, 1367, 1258, 1153, 1082 cm^{-1}; ES-MS: *m/z*: calcd for $C_{62}H_{62}N_4O_{14}Na$ $[M+Na]^+$: 1109.42, found: 1109.7, 135; $[\alpha]_D^{25}=-133$ ($c=1.0$ in $CHCl_3$).

A solution of DBU (0.72 mL, 4.80 mmol) and DMF (5.0 mL) was added to a solution of the above alcohol (2.60 g, 2.40 mmol), TESCl (1.40 g, 9.60 mmol), and DMF (10 mL) at rt. The resulting solution was maintained at rt for 1 h, and was then diluted with EtOAc (200 mL) and poured into aqueous 1M HCl (100 mL). The layers were separated and the organic layer was washed with 1M HCl (2 × 50 mL), saturated aqueous $NaHCO_3$ (1 × 50 mL), brine (1 × 50 mL), dried ($MgSO_4$), and concentrated. The crude residue was purified by chromatography on silica gel (8:1 hexanes/Et_2O then 3:1 hexanes/Et_2O then 1:1 Et_2O/hexanes then 3:1 Et_2O/hexanes) to give **60** (3.00 g, 95%) as a near colorless oil that was homogeneous by TLC analysis: ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=7.78$ (brs, 2H), 7.53 (d, $J=$ 8.2 Hz, 2H), 7.48 (s, 2H), 7.35–7.20 (m, 20H), 6.05 (brs, 2H), 5.40–4.60 (m, 8H), 3.95 (brs, 2H), 2.91 (dd, $J=12.3$, 7.2 Hz, 2H), 2.46 (dd, $J=12.3$, 10.6 Hz, 2H), 1.60–1.32 (brm, 18H), 0.74 (t, $J=7.8$ Hz, 18H), 0.40–0.20 (m, 12H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=170.6$, 153.0, 141.6, 137.7, 136.7, 136.0, 129.4, 128.3, 128.3, 128.1, 122.3, 118.2, 85.1, 81.6, 81.5, 67.4, 59.6, 38.4, 27.8, 6.5, 5.4; IR (film): $\tilde{\nu}=2955$, 2876, 1723, 1478, 1321, 1257, 1152, 1107 cm^{-1}; ES-MS: *m/z*: calcd for $C_{74}H_{90}N_4O_{14}Si_2Na$ $[M+Na]^+$: 1337.59, found: 1337.8, 135; $[\alpha]_D^{25}=-124$ ($c=1.0$ in $CHCl_3$).

3a-Triethylsiloxypyrroloindoline *tert*-butyl ester dimer 61: The same procedure for the preparation of **22** was used with the following amounts: **60** (2.70 g, 2.06 mmol) and 10% Pd/C (100 mg) in EtOAc (30.0 mL); pyridine (1.00 mL, 12.3 mmol), the crude residue, Fmoc-HOSu (2.77 g, 8.20 mmol), and CH_2Cl_2 (10 mL). The crude residue was purified by chromatography on silica gel (8:1 hexanes/Et_2O then 3:1 hexanes/Et_2O then 1:1 Et_2O/hexanes then 3:1 Et_2O/hexanes then Et_2O) to give **61** (2.41 g, 96%) as a light pink oil that was homogeneous by TLC analysis: ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=7.81-7.40$ (m, 20H), 6.70 (dd, $J=15.3$, 7.9 Hz, 0.8H), 6.38 (dd, $J=15.3$, 7.9 Hz, 1.2H), 5.56–5.48 (m, 1.6H), 4.79 (brs, 4H), 4.55–3.98 (m, 5.2H), 3.58–3.53 (m, 1.2H), 2.85–2.80 (m, 0.8H), 2.75–2.68 (m, 0.8H), 2.60–2.45 (m, 2.4H), 1.48–1.43 (m, 18H), 1.00–0.79 (m, 18H), 0.65–0.30 (m, 12H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=170.6$, 169.9, 154.8, 153.8, 147.5, 147.4, 146.8, 146.7, 144.0, 143.9, 143.8, 143.1, 141.6, 141.2, 141.0, 140.9, 132.5, 132.2, 130.2, 130.0, 129.9, 128.8, 128.4, 128.1, 128.0, 127.7, 127.6, 127.5, 127.3, 127.2, 126.9, 126.8, 126.7, 125.2, 124.9, 124.7, 124.4, 124.3, 121.9, 121.8, 121.7, 119.8, 119.7, 87.8, 87.4, 83.6, 82.7, 81.5, 81.1, 67.6, 65.9, 59.5, 59.3, 46.9, 43.5, 43.2, 27.8, 6.6, 6.5, 5.4, 5.3; IR (film): $\tilde{\nu}=3419$, 2954, 1744, 1712, 1481, 1296, 1151, 1109 cm^{-1}; ES-MS: *m/z*: calcd for $C_{72}H_{86}N_4O_{10}Si_2Na$ $[M+Na]^+$: 1245.58, found: 1245.9, 135; $[\alpha]_D^{25}=-216$ ($c=$ 1.0 in $CHCl_3$).

Pyrroloindoline allyl ester dimer 63: Neat TESOTf (3.80 mL, 16.4 mmol) was added to a 0 °C solution of **61** (1.00 g, 0.82 mmol), 2,6-lutidine (4.80 mL, 41.0 mmol), and CH_2Cl_2 (6 mL). The resulting solution was allowed to warm to rt overnight, recooled to 0 °C, quenched with saturated aqueous $NaHCO_3$ (50 mL), and diluted with EtOAc (100 mL). The layers were separated and the organic layer was washed with aqueous 1M HCl (2 × 50 mL), brine (1 × 50 mL), dried (Na_2SO_4), and concentrated to give crude diacid **62**. This residue residue was azeotroped with toluene (2 × 100 mL) to remove TESOH and was used without further purification.

A solution of DBAD (1.13 g, 4.91 mmol) and THF (10.0 mL) was added to a 0 °C solution of the crude residue, allyl alcohol (1.10 mL, 16.4 mmol), Ph_3P (1.72 g, 6.60 mmol), and THF (20.0 mL). The resulting solution was maintained at 0 °C for 2 h and then concentrated. The crude residue was purified by chromatography on silica gel (8:1 hexanes/Et_2O then 3:1 hexanes/Et_2O then 1:1 Et_2O/hexanes then 3:1 Et_2O/hexanes then Et_2O) to give **63** (792 mg, 81%) as a light purple oil that was homogeneous by TLC analysis: ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=7.85-7.21$ (m, 20H), 6.65 (dd, $J=13.7$, 8.0 Hz, 0.8H), 6.28 (dd, $J=13.7$, 8.1 Hz, 1.2H), 5.90–5.80 (m, 2H), 5.35–5.19 (m, 4H), 4.80–4.30 (m, 8H), 4.19–4.11 (m, 2H), 2.82–2.65 (m, 1.6H), 2.49–2.45 (m, 2.4H), 0.91–0.71 (m, 18H), 0.52–0.24 (m, 12H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=171.2$, 170.7, 154.9, 154.0, 147.4, 147.3, 146.9, 146.8, 144.0, 143.9, 143.4, 141.7, 141.2, 141.1, 141.0, 132.8, 132.4, 131.7, 131.6, 130.1, 129.7, 128.6, 128.3, 127.9, 127.7, 127.6, 127.5, 127.3, 127.0, 125.0, 124.9, 124.6, 124.4, 122.1, 122.0, 121.8, 120.0, 119.9, 118.7, 118.2, 110.6, 109.7, 88.1, 87.7, 83.8, 82.8, 67.7, 66.2, 65.9, 65.7, 59.0, 58.8, 47.1, 47.0, 43.8, 43.2, 28.1, 6.7, 6.6, 5.7, 5.5; IR (film): $\tilde{\nu}=3419$, 2953, 1751, 1711, 1420, 1296, 1154, 1110 cm^{-1}; ES-MS: *m/z*: calcd for $C_{70}H_{78}N_4O_{10}Si_2Na$ $[M+Na]^+$: 1213.52, found: 1213.9, 135; $[\alpha]_D^{25}=-205$ ($c=1.0$ in $CHCl_3$).

Pyrroloindoline dimer 64: The same procedure for the preparation of **24** was used with the following amounts: Piperidine (0.21 mL, 2.15 mmol), **63** (640 mg, 0.54 mmol), and CH_3CN (5.0 mL). The crude residue was purified by chromatography on silica gel (8:1 hexanes/Et_2O then 3:1 hexanes/Et_2O then 1:1 Et_2O/hexanes then 3:1 Et_2O/hexanes then Et_2O then EtOAc) to give **64** (297 mg, 74%) as a near colorless oil that was homogeneous by TLC analysis: ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=7.30$ (s, 2H), 7.21 (dd, $J=8.3$, 1.6 Hz, 2H), 6.54 (d, $J=8.2$ Hz, 2H), 5.84–5.72 (m, 2H), 5.22 (dd, $J=17.1$, 1.0 Hz, 2H), 5.13 (dd, $J=10.4$, 0.9 Hz, 2H), 4.95 (s, 2H), 4.60–4.45 (m, 4H), 3.67 (dd, $J=9.3$, 6.1 Hz, 2H), 2.50 (dd, $J=12.2$, 6.0 Hz, 2H), 2.38 (dd, $J=12.1$, 9.8 Hz, 2H), 0.80 (t, $J=$ 7.9 Hz, 18H), 0.51–0.15 (m, 12H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=173.0$, 148.7, 132.4, 131.5, 130.8, 128.1, 122.7, 118.3, 109.9, 91.1, 84.4, 65.4, 59.0, 46.9, 6.6, 5.5; IR (film): $\tilde{\nu}=3357$, 2952, 1737, 1618, 1482, 1123, 1086, 1009 cm^{-1}; ES-MS: *m/z*: calcd for $C_{40}H_{59}N_4O_6Si_2$ $[M+H]^+$: 741.38, found: 747.7, 135; $[\alpha]_D^{25}=-49.0$ ($c=$ 1.0 in $CHCl_3$).

***cis*-Hexadepsipeptide dimer (65)**: The same procedure for the preparation of **46** was used with the following amounts: HATU (509 mg, 1.34 mmol), **64** (250 mg, 0.34 mmol),

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45 (1.29 g, 1.34 mmol), HOAt (365 mg, 2.68 mmol), collidine (0.53 mL, 4.02 mmol), and CH_2Cl_2 (5.0 mL). The crude residue was purified by chromatography on silica gel (8:1 hexanes/Et_2O then 3:1 hexanes/Et_2O then 1:1 Et_2O/hexanes then 3:1 Et_2O/hexanes then Et_2O then EtOAc) to give **65** (535 mg, 60%) as a near colorless oil that was homogeneous by TLC analysis: ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.26-6.41$ (m, 12H), 5.95–5.58 (m, 6H), 5.41–4.20 (m, 24H), 3.81–3.35 (m, 2H), 2.85–2.50 (m, 8H), 2.40–2.05 (m, 6H), 1.82–1.48 (m, 8H), 1.21–0.65 (m, 96H), 0.59–0.34 (m, 12H), 0.18– −0.15 (m, 24H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 174.0$, 172.3, 172.1, 171.7, 171.4, 170.9, 170.8, 169.8, 168.0, 167.8, 166.6, 154.2, 154.1, 153.5, 146.1, 145.5, 131.9, 131.8, 131.5, 131.3, 130.9, 129.6, 129.2, 127.9, 127.6, 125.3, 120.8, 119.0, 118.6, 118.2, 109.6, 109.3, 95.4, 95.3, 95.1, 88.2, 87.9, 86.1, 85.9, 76.4, 75.8, 74.4, 74.3, 68.0, 67.8, 66.1, 65.8, 65.4, 62.0, 59.9, 59.8, 59.5, 59.1, 53.9, 51.0, 49.2, 48.9, 46.6, 45.9, 45.7, 43.5, 43.3, 43.2, 32.4, 31.4, 30.3, 30.1, 29.3, 29.2, 25.9, 25.8, 25.6, 24.4, 24.3, 23.0, 22.2, 21.9, 21.7, 21.5, 19.2, 18.8, 18.7, 18.4, 18.0, 17.9, 17.8, 17.6, 17.5, 17.4, 17.1, 6.6, 6.5, 5.8, 5.6, −4.2, −4.6, −4.9, −5.0, −5.2, −5.3, −5.6, −5.7; IR (film): $\tilde{\nu} = 3382$, 2932, 1743, 1668, 1510, 1252, 1118, 834 cm^{-1}; ES-MS: *m*/*z*: calcd for $C_{120}H_{202}Cl_6N_{14}O_{26}Si_6Na$ $[M+Na]^+$: 2656.16, found: 2656.5, 135; $[\alpha]_D^{25} = -15.4$ ($c = 1.0$ in $CHCl_3$).

***cis*-Hexadepsipeptide carboxylic acid dimer 66**: The same procedure for the preparation of **47** was used with the following amounts: $PhSiH_3$ (0.18 mL, 1.48 mmol), **65** (650 mg, 0.25 mmol), $[Pd(Ph_3P)_4]$ (50 mg), and THF (5 mL). The crude residue was purified by chromatography on silica gel (8:1 hexanes/Et_2O then 3:1 hexanes/Et_2O then 1:1 Et_2O/hexanes then 3:1 Et_2O/hexanes then Et_2O then EtOAc) to give **66** (510 mg, 81%) as a colorless oil that was homogeneous by TLC analysis: ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.41-6.36$ (m, 12H), 5.80–5.42 (m, 4H), 5.30–4.20 (m, 16H), 3.87–3.75 (m, 2H), 2.90–2.10 (m, 14H), 1.80–1.41 (m, 8H), 1.20–0.62 (m, 96H), 0.59–0.39 (m, 12H), 0.16– −0.18 (m, 24H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 173.6$, 173.1, 172.5, 172.1, 171.7, 171.3, 171.1, 171.0, 170.0, 168.8, 168.1, 155.0, 154.2, 153.6, 145.0, 131.9, 129.5, 129.3, 127.5, 121.1, 109.7, 95.3, 95.1, 95.0, 94.5, 89.5, 88.4, 88.2, 86.3, 83.2, 74.9, 74.6, 74.5, 67.8, 62.2, 60.3, 59.4, 58.9, 54.6, 54.0, 49.2, 48.9, 45.7, 43.4, 34.5, 34.1, 32.6, 32.1, 31.6, 31.2, 30.2, 29.9, 29.5, 29.3, 29.2, 26.0, 25.8, 25.8, 25.6, 25.5, 24.4, 23.2, 23.0, 22.8, 22.4, 21.6, 21.3, 20.8, 19.4, 19.2, 18.9, 18.8, 18.6, 18.3, 18.0, 17.9, 17.8, 17.5, 17.4, 17.1, 16.8, 14.0, 13.9, 6.7, 6.6, 5.9, 5.8, 5.7, 5.6, −4.9, −5.0, −5.1, −5.7; IR (film): $\tilde{\nu} = 3381$, 2956, 1730, 1667, 1650, 1514, 1253, 1120, 756 cm^{-1}; ES-MS: *m*/*z*: calcd for $C_{114}H_{194}Cl_6N_{14}O_{26}Si_6Na$ $[M+Na]^+$: 2576.09, found: 2576.4, 135; $[\alpha]_D^{25} = -28.9$ ($c = 1.0$ in $CHCl_3$).

Himastatin (68): Pb/Cd couple (300 mg) was added to a vigorously stirred mixture of **66** (385 mg, 0.15 mmol), THF (5.0 mL), and aqueous 1M NH_4OAc (5.0 mL). After 1.5 h, the layers were separated and the aqueous layer was extracted with EtOAc (4 × 5 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. This crude amino acid (330 mg, ≈100%) was split into two equal batches and used without further purification.

HATU (110 mg, 0.29 mmol) was added to a solution of the crude amino acid (≈165 mg), HOAt (79.0 mg, 0.58 mmol), *i*Pr_2NEt (0.15 mL, 0.87 mmol), and DMF (50 mL) at rt. The resulting solution was maintained at rt for 28 h and then concentrated. The resulting crude residue was dissolved in EtOAc (10 mL) and washed with aqueous 1M HCl (3 × 5 mL), saturated aqueous $NaHCO_3$ (3 × 5 mL), brine (1 × 5 mL), dried (Na_2SO_4), and concentrated. The two batches of cyclic dimer (≈165 mg each) were recombined at this stage and used without further purification.

A solution of TBAF (1M in THF, 5.80 mL) was added to a 0 °C solution of the crude residue (≈330 mg), HOAc (1.00 mL, 17.4 mmol), and THF (3.0 mL). The resulting solution was allowed to warm to rt, maintained at rt for 55 h, and then diluted with EtOAc (10 mL) and quenched with saturated aqueous $NaHCO_3$ (10 mL). The layers were separated and the organic layer was washed with aqueous 1M HCl (8 × 5 mL), saturated aqueous $NaHCO_3$ (8 × 5 mL), brine (8 × 5 mL), dried (Na_2SO_4), and concentrated. The crude residue was purified by chromatography on silica gel (Et_2O then EtOAc then $CHCl_3$ then 1% MeOH/$CHCl_3$ then 2% MeOH/$CHCl_3$ then 10% MeOH/$CHCl_3$) to give **68** (76.7 mg, 34%) as a colorless solid that was homogeneous by TLC analysis. M.p. > 360 °C (dec); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.58$ (s, 2H), 7.43–7.41 (m, 4H), 7.28 (d, $J = 10.0$ Hz, 2H), 7.11 (d, $J = 10.4$ Hz, 2H), 6.79 (d, $J = 8.3$ Hz, 2H), 5.91 (s, 2H), 5.81 (br s, 2H), 5.63 (d, $J = 8.6$ Hz, 2H), 5.42 (d, $J = 12.3$ Hz, 2H), 5.30–5.20 (m, 4H), 5.14–5.12 (m, 4H), 4.98 (d, $J = 10.5$ Hz, 2H), 4.89 (dd, $J = 9.9$, 3.0 Hz, 2H), 4.50–4.44 (m, 2H), 4.25–4.21 (m, 2H), 3.82 (s, 2H), 3.62 (s, 2H), 3.06 (d, $J = 13.1$ Hz, 2H), 2.85 (t, $J = 13.5$ Hz, 2H), 2.76 (d, $J = 14.3$ Hz, 2H), 2.60–2.50 (m, 2H), 2.48 (d, $J = 14.8$ Hz, 2H), 2.25–2.10 (m, 4H), 1.98–1.90 (m, 2H), 1.72–1.65 (m, 6H), 1.41–1.35 (m, 2H), 1.15 (d, $J = 6.5$ Hz, 6H), 1.11 (d, $J = 6.6$ Hz, 6H), 1.02 (d, $J = 6.5$ Hz, 6H), 1.00 (d, $J = 6.6$ Hz, 6H), 0.92 (d, $J = 5.7$ Hz, 6H), 0.87 (d, $J = 6.7$ Hz, 6H), 0.85 (d, $J = 6.5$ Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 174.1$, 173.9, 173.4, 173.2, 173.0, 172.3, 146.6, 134.3, 132.2, 128.4, 121.3, 112.6, 90.8, 86.2, 66.7, 60.8, 58.7, 57.1, 54.3, 53.8, 52.6, 49.9, 40.9, 39.4, 30.0, 29.9, 28.6, 25.3, 23.0, 21.0, 19.3, 18.9, 18.3, 17.3, 16.4; IR (film): $\tilde{\nu} = 3392$, 2238, 2963, 1725, 1671, 1624, 1535, 1417, 1246, 1154, 914 cm^{-1}; ES-MS: *m*/*z*: calcd for $C_{72}H_{104}N_{14}O_{20}Na$ $[M+Na]^+$: 1507.74, found: 1508.2, 135; $[\alpha]_D^{25} = -33.8$ ($c = 0.35$ in MeOH).

Fmoc-Pyrroloindoline 70: Neat pyridine (5.30 mL, 65.2 mmol) was added to a 0 °C solution of **14** (3.00 g, 10.9 mmol), Fmoc-HOSu (7.30 g, 21.7 mmol), and CH_2Cl_2 (75 mL). The resulting solution was allowed to warm to rt overnight and then concentrated. The crude residue was purified by chromatography on silica gel (8:1 hexanes/Et_2O then 3:1 hexanes/Et_2O then 1:1 Et_2O/hexanes then 3:1 Et_2O/hexanes) to give **70** (3.00 g, 55%) as a colorless solid that was homogeneous by TLC analysis: m.p. 157–158.5 °C; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.81-7.10$ (m, 10H), 6.80 (t, $J = 7.4$ Hz, 0.30H), 6.75 (t, $J = 7.4$ Hz, 0.70H), 6.63 (d, $J = 7.9$ Hz, 0.30H), 6.36 (d, $J = 7.9$ Hz, 0.70H), 5.60 (s, 0.30H), 4.94 (s, 0.70H), 4.78 (dd, $J = 10.6$, 4.4 Hz, 0.70H), 4.72 (dd, $J = 10.6$, 3.9, 0.70H), 4.57–4.40 (m, 0.60H), 4.38–4.24 (m, 1H), 4.21–4.15 (m, 1H), 3.22 (s, 0.30H), 3.17 (s, 0.70H), 2.63 (dd, $J = 13.8$, 9.0 Hz, 0.35H), 2.54 (dd, $J = 13.8$, 3.2 Hz, 0.35H), 2.35–2.24 (m, 1.3H), 1.48 (s, 3H), 1.47 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 172.9$, 172.7, 155.0, 154.2, 147.9, 147.5, 144.0, 143.9, 143.8, 143.2, 141.6, 141.2, 141.2, 141.1, 130.2, 129.9, 129.8, 129.5, 127.8, 127.5, 127.3, 127.1, 127.0, 125.3, 125.0, 124.7, 124.4, 123.0, 122.8, 120.0, 119.9, 119.5, 119.2, 110.5, 109.9, 87.7, 86.9, 85.8, 85.1, 82.7, 82.6, 68.1, 66.2, 60.7, 60.6, 47.1, 42.2, 41.3, 27.9, 27.8; IR (film): $\tilde{\nu} = 3417$, 2978, 1708, 1612, 1154, 755 cm^{-1}; ES-MS: *m*/*z*: calcd for $C_{30}H_{30}N_2O_5Na$ $[M+Na]^+$: 521.21, found: 521.4, 135; $[\alpha]_D^{25} = -111$ ($c = 1.0$ in $CHCl_3$).

Pyrroloindoline allyl ester 71: Neat TESOTf (8.30 mL, 36.1 mmol) was added to a 0 °C solution of **70** (1.80 g, 3.61 mmol), 2,6-lutidine (8.40 mL, 72.2 mmol), and CH_2Cl_2 (12 mL). The resulting solution was allowed to warm to rt overnight and then quenched with saturated aqueous $NaHCO_3$ (100 mL) and diluted with EtOAc (100 mL). The layers were separated and the organic layer was washed with aqueous 1M HCl (2 × 50 mL), brine (1 × 50 mL), dried (Na_2SO_4), and concentrated.

A solution of DBAD (1.60 g, 7.20 mol) and THF (5 mL) was added to a 0 °C solution of the crude carboxylic acid, allyl alcohol (2.50 mL, 36.1 mmol), Ph_3P (1.90 g, 7.20 mmol), and THF (15 mL). The resulting solution was maintained at 0 °C for 1.5 h and then concentrated. The crude residue was purified by chromatography on silica gel (8:1 hexanes/Et_2O then 3:1 hexanes/Et_2O then 1:1 Et_2O/hexanes then 3:1 Et_2O/hexanes then Et_2O) to give the allyl ester as a colorless oil contaminated by bis-Boc hydrazine.

Piperidine (1.43 mL, 14.4 mmol) was added to a solution of this semi-purified residue and CH_3CN (15 mL) at rt. After 1.5 h, the resulting mixture was concentrated. The crude residue was purified by chromatography on silica gel (8:1 hexanes/Et_2O then 3:1 hexanes/Et_2O then 1:1 Et_2O/hexanes then 3:1 Et_2O/hexanes then Et_2O) to give **71** (603 mg, 46%) as a colorless oil that was homogeneous by TLC analysis: ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.21$ (d, $J = 7.5$ Hz, 1H), 7.12 (dt, $J = 7.8$, 1.2 Hz, 1H), 6.76 (dt, $J = 7.4$, 0.8 Hz, 1H), 6.58 (d, $J = 7.9$ Hz, 1H), 5.92–5.84 (m, 1H), 5.30 (dd, $J = 17.2$, 1.4 Hz, 1H), 5.22 (dd, $J = 10.4$, 1.2 Hz, 1H), 5.22 (s, 1H), 4.65–4.61 (m, 2H), 4.32 (br s, 1H), 3.71 (dd, $J = 9.6$, 6.1 Hz, 1H), 2.58 (dd, $J = 12.4$,

6.1 Hz, 1H), 2.44 (dd, $J = 12.6$, 9.6 Hz, 1H), 0.82 (t, $J = 3.5$ Hz, 9H), 0.46 – 0.30 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 172.9$, 150.0, 131.5, 130.1, 129.6, 124.3, 118.3, 118.2, 109.5, 90.9, 83.9, 65.2, 58.9, 46.7, 6.5, 5.4; IR (film): $\tilde{\nu} = 3349$, 2911, 1737, 1611, 1470, 1132, 742 cm^{-1}; ES-MS: m/z: calcd for $C_{20}H_{31}N_2O_3Si$ $[M+Na]^+$: 375.19, found: 375.3, 135; $[\alpha]_D^{25} = -98.2$ ($c = 1.0$ in $CHCl_3$).

***cis*-Hexadepsipeptide monomer 72**: The same procedure for the preparation of **46** was used with the following amounts: HATU (101 mg, 0.27 mmol), **71** (122 mg, 0.13 mmol), acid **45** (75 mg, 0.065 mmol), HOAt (72.0 mg, 0.53 mmol), collidine (0.11 mL, 0.80 mmol), and CH_2Cl_2 (1.0 mL). The crude residue was purified by chromatography on silica gel (8:1 hexanes/Et_2O then 3:1 hexanes/Et_2O then 1:1 Et_2O/hexanes then 3:1 Et_2O/hexanes then Et_2O) to give **72** (85.0 mg, 52%) as a colorless oil that was homogeneous by TLC analysis: ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.24$ – 6.20 (m, 7H), 5.98 – 5.80 (m, 1H), 5.65 – 4.20 (m, 15H), 3.82 – 3.70 (m, 1H), 2.85 – 2.60 (m, 4H), 2.38 – 2.04 (m, 4H), 1.80 – 1.55 (m, 3H), 1.21 – 0.60 (m, 48H), 0.45 – 0.30 (m, 6H), 0.18 – – 0.10 (m, 12H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 172.4$, 172.2, 171.9, 171.5, 171.0, 170.9, 168.0, 167.9, 154.3, 146.8, 131.6, 129.5, 122.7, 122.5, 119.2, 118.8, 118.2, 117.3, 109.5, 95.4, 88.0, 86.1, 76.5, 74.5, 68.1, 67.9, 66.2, 66.0, 65.8, 65.6, 62.1, 60.1, 59.9, 59.6, 59.2, 55.8, 54.1, 54.0, 51.1, 49.3, 49.0, 46.1, 45.9, 43.5, 32.5, 31.5, 30.4, 30.2, 29.5, 29.3, 28.1, 26.0, 25.9, 25.7, 25.5, 24.6, 24.5, 23.2, 22.8, 22.3, 22.0, 21.8, 21.7, 19.3, 19.0, 18.8, 18.2, 18.0, 17.9, 17.7, 17.6, 17.2, 15.2, – 4.2, – 4.8, – 4.9, – 5.0, – 5.2, – 5.6; IR (film): $\tilde{\nu} = 3382$, 2932, 1738, 1671, 1112, 834, 753 cm^{-1}; ES-MS: m/z: calcd for $C_{60}H_{102}Cl_3N_7O_{13}Si_3Na$ $[M+Na]^+$: 1340.58, found: 1340.8, 135; $[\alpha]_D^{25} = -31.0$ ($c = 0.7$ in $CHCl_3$).

***cis*-Hexadepsipeptide carboxylic acid monomer 73**: The same procedure for the preparation of **47** was used with the following amounts: $PhSiH_3$ (15.0 μL, 0.12 mmol), **72** (80.0 mg, 0.061 mmol), $[Pd(Ph_3P)_4]$ (10 mg), and THF (1.50 mL). The crude residue was purified by chromatography on silica gel (3:1 hexanes/Et_2O then 1:1 Et_2O/hexanes then 3:1 Et_2O/hexanes then Et_2O) to give **73** (71.1 mg, 92%) as a colorless oil that was homogeneous by TLC analysis: ^{1}H NMR (500 MHz, $CDCl_3$): $\delta =$ 7.40 – 6.40 (m, 7H), 5.78 – 5.48 (m, 2H), 5.10 – 4.05 (m, 8H), 3.91 – 3.74 (m, 1H), 2.95 – 2.51 (m, 5H), 2.40 – 2.08 (m, 3H), 1.85 – 1.42 (m, 3H), 1.20 – 0.75 (m, 48H), 0.58 – 0.39 (m, 6H), 0.32 – – 0.11 (m, 12H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 173.8$, 173.2, 172.4, 172.2, 172.1, 172.0, 171.8, 171.5, 171.4, 171.1, 170.8, 169.9, 169.0, 169.2, 168.2, 134.2, 131.5, 130.5, 130.4, 130.2, 129.7, 129.0, 127.7, 124.0, 123.5, 122.8, 121.1, 119.5, 118.3, 112.7, 110.6, 109.6, 95.4, 95.1, 94.6, 89.6, 88.1, 86.4, 83.4, 83.0, 75.0, 74.9, 74.6, 71.0, 69.7, 68.1, 67.9, 65.8, 62.3, 62.2, 60.7, 59.9, 59.7, 59.4, 59.2, 58.2, 55.3, 54.7, 54.2, 54.0, 53.4, 52.0, 51.3, 49.4, 49.2, 45.9, 43.3, 43.1, 42.0, 41.8, 39.5, 32.2, 31.6, 30.6, 30.3, 29.6, 29.3, 29.2, 28.1, 26.2, 26.1, 26.0, 25.9, 25.6, 25.5, 24.7, 23.1, 23.0, 21.8, 21.0, 19.3, 19.1, 19.0, 18.8, 18.3, 18.2, 18.1, 18.0, 17.7, 17.5, 17.3, 16.8, 6.7, 5.9, 5.8, 5.7, 5.5, – 4.7, – 4.8, – 4.9, – 5.1, – 5.4, – 5.6; IR (film): $\tilde{\nu} = 3380$, 2956, 1732, 1668, 1254, 1116, 835 cm^{-1}; ES-MS: m/z: calcd for $C_{57}H_{98}Cl_3N_7O_{13}Si_3Na$ $[M+Na]^+$: 1300.55, found: 1300.7, 135; $[\alpha]_D^{25} = -39.3$ ($c = 0.35$ in $CHCl_3$).

***cis*-Cyclic monomer 74**: The same procedure for the preparation of **68** was used with the following amounts: Pb/Cd couple (100 mg), **73** (55.0 mg, 0.043 mmol), THF (3 mL), and aqueous 1M NH_4OAc (3 mL); HATU (24.0 mg, 0.064), the crude amino acid (47.0 mg), HOAt (17.0 mg, 0.13 mmol), iPr_2NEt (22.0 μL, 0.13 mmol), and DMF (26 mL); TBAF (1M in THF, 0.84 mL), the crude cyclic monomer (≈ 50 mg), HOAc (0.14 mL, 0.24 mmol), and THF (3.0 mL). The crude residue was purified by chromatography on silica gel (3:1 hexanes/Et_2O then 1:1 Et_2O/hexanes then 3:1 Et_2O/hexanes then Et_2O) to give **74** (25.0 mg, 78%) as a colorless solid that was homogeneous by TLC analysis: m.p. > 260 °C (dec); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.41$ (d, $J = 4.8$ Hz, 1H), 7.33 (d, $J = 7.4$ Hz, 1H), 7.29 (d, $J = 10.0$ Hz, 1H), 7.19 (t, $J = 7.6$ Hz, 1H), 7.10 (d, $J = 10.4$ Hz, 1H), 6.89 (t, $J = 7.4$ Hz, 1H), 6.76 (d, $J = 7.9$ Hz, 1H), 5.85 (s, 1H), 5.80 (br s, 1H), 5.63 (d, $J = 8.6$ Hz, 1H), 5.41 (d, $J =$ 12.6 Hz, 1H), 5.20 – 5.18 (m, 2H), 5.13 – 5.10 (m, 2H), 4.96 (d, $J = 10.5$ Hz, 1H), 4.89 (dd, $J = 9.9$, 2.9 Hz, 1H), 4.45 – 4.40 (m, 1H), 4.28 – 4.23 (m, 1H), 3.81 (s, 1H), 3.61 (s, 1H), 3.06 (d, $J = 14.0$ Hz, 1H), 2.83 (t, $J = 13.2$ Hz, 1H), 2.74 (d, $J = 14.3$ Hz, 1H), 2.60 – 2.50 (m, 1H), 2.48 (d, $J = 15.1$ Hz, 1H), 2.25 – 2.10 (m, 2H), 2.00 – 1.88 (m, 1H), 1.80 – 1.62 (m, 3H), 1.42 – 1.35 (m, 1H), 1.15 (d, $J = 6.5$ Hz, 3H), 1.11 (d, $J = 6.6$ Hz, 3H), 1.00 (d, $J =$ 6.8 Hz, 6H), 0.91 (d, $J = 5.6$ Hz, 3H), 0.86 (d, $J = 6.5$ Hz, 3H), 0.85 (d, $J =$ 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 174.1$, 173.9, 173.4, 173.2, 173.0, 172.3, 147.7, 131.7, 129.8, 123.2, 121.0, 112.3, 90.8, 85.9, 66.6, 60.7, 58.6, 57.2, 54.2, 53.8, 52.6, 49.9, 40.9, 39.4, 30.0, 29.9, 28.6, 25.2, 22.9, 20.9, 19.3, 18.9, 18.2, 17.3, 16.4; IR (film): $\tilde{\nu} = 3390$, 3328, 2963, 1724, 1673, 1642, 1530, 1250, 1153, 753 cm^{-1}; ES-MS: m/z: calcd for $C_{36}H_{53}N_7O_{10}Na$ $[M+Na]^+$: 766.38, found: 766.5, 135; $[\alpha]_D^{25} = +37.5$ ($c = 0.7$ in $CHCl_3$).

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